Message

From: EPA Press Office [press=epa.gov@cmail19.com]
on behalf of EPA Press Office [press@epa.gov]
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To: Harlow, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b5a9a34e31fc4fe6b2beaddda2affa44-Harlow, Dav]
Subject: EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

U.S. ENVIRONMENTAL PROTECTION AGENCY
NEWS RELEASE
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EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

WASHINGTON (April 24, 2018) - Today, U.S. Environmental Protection Agency (EPA) Administrator Scott Pruitt signed a proposed rule to strengthen the science used in regulations issued by EPA. The rule will ensure that the regulatory science underlying Agency actions is fully transparent, and that underlying scientific information is publicly available in a manner sufficient for independent validation.

"The era of secret science at EPA is coming to an end," **said EPA Administrator Scott Pruitt.** "The ability to test, authenticate, and reproduce scientific findings is vital for the integrity of rulemaking process. Americans deserve to assess the legitimacy of the science underpinning EPA decisions that may impact their lives."

This proposed rule is in line with the scientific community's moves toward increased data sharing to address the "replication crisis"—a growing recognition that a significant proportion of published research may not be reproducible. The proposal is consistent with data access requirements for major scientific journals like *Science*, *Nature*, and *Proceedings of the National Academy of Sciences* as well as recommendations from the Bipartisan Policy Center's Science for Policy Project and the Administrative Conference of the United States' Science in the Administrative Process Project.

The proposed rule builds upon President Trump's executive orders on regulatory reform and energy independence:

- **Executive Order 13777**, issued in March 2017, provides that regulatory reform efforts shall attempt to identify "those regulations that rely in whole or in part on data, information, or methods that are not publicly available or that are insufficiently transparent to meet the standard of reproducibility."
- **Executive Order 13783**, also issued in March 2017, provides that "It is the policy of the United States that necessary and appropriate environmental regulations comply with the law, are of greater benefit than cost, when permissible, achieve environmental improvements for the American people, and are developed through transparent processes that employ the best available peer-reviewed science and economics."

Chairman Lamar Smith (R-TX): "Administrator Pruitt's announcement ensures that data will be secret no more. For too long, the EPA has issued rules and regulations based on data that has been withheld from the American people. It's likely that in the past, the data did not justify all regulations. Today, Administrator Pruitt rightfully is changing business as usual and putting a stop to hidden agendas."

Senator Mike Rounds (R-SD): "Sound, reliable science is vital to helping us make important policy decisions that impact the health of American families and their livelihoods. Inserting new levels of transparency in the EPA rulemaking process will help make the agency more accountable to the American people and help everyone understand the impact of EPA's decisions. Today's directive is a significant step toward making sure these decisions are not made behind closed doors with information accessible only to those writing the regulations, but rather in the full view of those who will be affected."

Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts: "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process."

Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the Journal *Risk Analysis*: "I believe that transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science. Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."

Dr. Jason Scott Johnston, Director, Olin Law and Economics Program, University of Virginia School of Law: "EPA's proposed rule, Strengthening Transparency in Regulatory

Science, is badly needed "Best practice among peer-edited scientific journals is to require that data and statistical routines used in published papers be posted online and/or made publicly available. To apply the same standards to research that EPA says justify regulations affecting billions of dollars in economic activity and millions of human lives is essential for those regulations to truly be scientifically based."

Bruno Pigott, Commissioner of the Indiana Department of Environmental Management (IDEM): "IDEM supports transparency in rulemaking. Good, sound science leads to better regulations."

Dr. George Wolff, Principal Scientist, Air Improvement Resource, Inc., and former Chairman of EPA's Clean Air Scientific Advisory Committee (1992 - 1996): "In the development of regulations based on environmental studies, numerous subjective assumptions and choices must be made regarding the selection of data and models that have a profound impact on the strength of any statistical associations and even whether the associations are positive or negative. The appropriateness of the assumptions and choices are not adequately evaluated in the standard peer review process. That is why it is essential that the data and models be placed in the public domain for a more rigorous evaluation by qualified experts. The proposed regulation, Strengthening Transparency in Regulatory Science, will provide an opportunity for such evaluations."

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U.S. Environmental Protection Agency
1200 Pennsylvania Avenue Northwest
Washington, D.C. 20004

Message

From: Harlow, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B5A9A34E31FC4FE6B2BEADDDA2AFFA44-HARLOW, DAV]
Sent: 7/10/2018 10:00:12 PM
To: Yamada, Richard (Yujiro) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4c34a1e0345e4d26b361b5031430639d-Yamada, Yuj]
CC: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: Paper
Attachments: 1559325818779651.pdf

Richard,

Here you go.

David S. Harlow
Senior Counsel
Immediate Office of the Assistant Administrator
Office of Air and Radiation, USEPA
WJC-N Room 5409K
1200 Pennsylvania Avenue NW
Washington, DC 20460
202-564-1233
Harlow.David@epa.gov

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It Is Time to Move Beyond the Linear No-Threshold Theory for Low-Dose Radiation Protection

John J. Cardarelli II[1] and Brant A. Ulsh[2]

Abstract

The US Environmental Protection Agency (USEPA) is the primary federal agency responsible for promulgating regulations and policies to protect people and the environment from ionizing radiation. Currently, the USEPA uses the linear no-threshold (LNT) model to estimate cancer risks and determine cleanup levels in radiologically contaminated environments. The LNT model implies that there is no safe dose of ionizing radiation; however, adverse effects from low dose, low-dose rate (LDDR) exposures are not detectable. This article (1) provides the scientific basis for discontinuing use of the LNT model in LDDR radiation environments, (2) shows that there is no scientific consensus for using the LNT model, (3) identifies USEPA reliance on outdated scientific information, and (4) identifies regulatory reliance on incomplete evaluations of recent data contradicting the LNT. It is the time to reconsider the use of the LNT model in LDDR radiation environments. Incorporating the latest science into the regulatory process for risk assessment will (1) ensure science remains the foundation for decision making, (2) reduce unnecessary burdens of costly cleanups, (3) educate the public on the real effects of LDDR radiation exposures, and (4) harmonize government policies with the rest of the radiation scientific community.

Keywords

LNT, risk assessment, threshold, radiation, dose–response, hormesis

Introduction

The US Environmental Protection Agency (USEPA) was established in 1970 and gained authority to promulgate environmental standards to limit man-made radioactive materials in the environment and develop national radiation protection guidance for Federal and State agencies.[1] Congress enacted several statutes providing USEPA the authority to regulate hazardous materials (eg, Clean Air Act, Safe Drinking Water Act, and the Comprehensive Environmental Response Compensation and Liability Act), including both chemical and radiological hazards.[2] Among many federal programs whose regulatory authorities were transferred to the USEPA, the Public Health Service Act (PHSA) authorities are of particular interest in this article. The PHSA authorities give the USEPA the ability to conduct monitoring of environmental radiation, perform research on the environmental and human health effects of exposure to radiation, and provide technical assistance to states and other federal agencies. These authorities are consistent with the mission of the USEPA to protect human health and the environment.

This article examines the radiation protection framework and policies of the USEPA as they are applied to low-dose, low-dose rate (LDDR) radiation exposures. It focuses on current scientific literature, policy implications, public health impacts, and future directions for developing a radiation protection framework based on sound scientific principles.

In this article, we refer to dose in Gy (or mGy), unless citing a direct quote that uses other units. Low-dose throughout this report is arbitrarily defined as a dose of 100 mGy (10 rad) above natural background. Low-dose rate is defined as <0.01 mGy/min (1 mrad/min) above natural

[1] Captain US Public Health Service Officer, Cincinnati, OH, USA
[2] M. H. Chew & Associates, Livermore, CA, USA

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Corresponding Author:
John J. Cardarelli II, Captain US Public Health Service Officer, 3840 Palmer Court, Cincinnati, OH, USA 45245.
Email: jjcardarelli2@gmail.com

background. The definitions for LDDRs have varied over time but generally fall below 200 mGy for low-dose and <0.05 mGy/min for low-dose rate.[3]

The USEPA relies on the linear no-threshold (LNT) dose–response model developed in the US National Academy of Sciences (NAS) biological effects of ionizing radiation VII report[4] to (1) set regulatory standards to protect human health,[5] (2) project risks of LDDR radiation exposure among the US population, and (3) develop tools to help establish cleanup levels.[6] We critically review the latest scientific literature and present alternative risk assessment models (eg, threshold or hormesis) for determining radiological cleanup levels in environments containing low-level residual radioactivity. Throughout this article, we note USEPA's public policy positions for radiation protection and suggest alternative risk assessment approaches that are consistent with the latest science, protective of human health and the environment, and reduce unnecessary public health and financial burdens to society affected by low-level residual contamination from man-made or natural radioactive materials.

Two recent petitions to US regulators have drawn increased attention to this issue. In 2015, several members of the group, Scientists for Accurate Information (SARI), submitted petitions[7,8] to the US Nuclear Regulatory Commission (NRC), requesting "... that the NRC greatly simplify and change Part 20 to eliminate the use of the LNT paradigm and take radiation hormesis into account." This petition cited 36 references in support of the petitioners' request. The bases of the petition were also presented in a peer-reviewed scientific article.[9] The USEPA submitted comments opposing the petition[10]; however, the USEPA's comments declined to address all but 2 references cited by the petitioners. The SARI also recently submitted a letter to the current administrator of the USEPA,[11] requesting that USEPA cease the application of the LNT for LDDR environments. The USEPA's response[12] cited its comments on the NRC petition.

Another recent event relevant to this topic is the issuance of Executive Order 13777[13] by the President of the United States. This Executive Order established a policy to eliminate unnecessary regulatory burdens. As a result, the USEPA formed a Regulatory Reform Task Force to evaluate existing regulations and identify regulations that should be repealed, replaced, or modified. The USEPA administrator advised the Office of Air and Radiation (OAR) to provide recommendations regarding specific rules that could be repealed, replaced, or modified to make them less burdensome by May 15, 2017. The OAR hosted a public meeting on April 24, 2017, to solicit proposals. The Health Physics Society (HPS) gave verbal comments during the meeting urging USEPA to reconsider their adherence to LNT and to improve several documents (eg,[6,14-17]) by better addressing uncertainties in LDDR environments. The HPS also stated that reliance on the LNT model "...tends to foment the public's fear of all types of radiation." The HPS followed up with written comments, which stated,

> As a scientific organization of professionals who specialize in radiation safety, the HPS believes the EPA's reliance on the LNT model, especially at very low doses and dose rates, is inappropriate and can exaggerate the risk. Of most concern to the HPS is the EPA's extrapolation of the LNT model to calculate collective dose and the use of collective dose as a metric for risk.[18,19]

This article is divided into sections addressing several questions regarding the continued use of the LNT model for LDDR radiation environments:

I. Introduction
II. What is the scientific basis for using the LNT in LDDR radiation environments?
III. Is the USEPA using the concept of collective dose appropriately?
IV. Is there scientific consensus for using the LNT model to estimate risk in LDDR environments?
V. Should the BEIR VII report continue to be used to justify the use of the LNT model for LDDR radiation environments?
VI. What other information is available in the scientific literature and does it support the continued use of the LNT model for LDDR environments?
VII. Is it appropriate to regulate ionizing radiation in the same manner as toxic chemicals?
VIII. Should the current USEPA regulatory radiation policies be reconsidered and harmonized with the radiation protection philosophy given the lessons learned from Fukushima?
IX. Discussion
X. Conclusion

What is the Scientific Basis for Using the LNT in LDDR Radiation Environments?

Studies to understand health effects on people exposed to LDDR are especially important, since they most closely reflect the environment following a radiological cleanup effort. They also serve to help regulatory agencies determine whether the cleanup policies are adequate to protect the people and environment while accounting for social and economic factors (ie, do they do more good than harm to society?). Does the LNT model withstand scientific scrutiny to link cancer with causation from LDDR exposures to ionizing radiation? Over 50 years ago, Sir Austin Bradford Hill established a set of objective criteria that help determine when causation can be legitimately concluded from an observed correlation.[20] These criteria are (1) temporal relationship (eg, exposure must occur before the disease), (2) strength (eg, size of the association between exposure and disease), (3) dose–response relationship, (4) consistency, (5) plausibility, (6) consideration of alternate explanation (eg, confounding effects), (7) experiment (eg, the condition can be altered by an appropriate experimental regimen), (8) specificity, and (9) coherence (eg, associated

compatible with existing theory and knowledge?). Hill's criteria have been specifically applied to LDDR,[21] and the case for LDDR increasing carcinogenic risk has been found lacking. In the current article, we point out when any of Hill's criteria can be applied to particular arguments or evidence.

In its comments on SARI's petition to the NRC, the USEPA stated,

> The U.S. Environmental Protection Agency strongly disagrees with the petition to the Nuclear Regulatory Commission (NRC) to cease using the linear no-threshold (LNT) model as a basis for regulating exposures to ionizing radiation. The USEPA's Carcinogen Assessment Guidelines specify that LNT should be used as a default assumption unless there is compelling evidence that the biological mechanism for carcinogenesis is inconsistent with LNT.[10]

This argument was also published by a senior official within the USEPA in a scientific article using a disclaimer that the article represented his own personal opinion. However, his article continues to be used by the agency to justify reliance on the LNT model. Puskin wrote:

> Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis . . .[5]

These explanations are not consistent with basic scientific study designs that accept a null hypothesis (eg, no effect at low doses[22]), unless there is strong evidence (eg, statistical significance $P < .05$) to suggest otherwise (eg, LNT is valid at low doses). *The burden of proof lies with those asserting the LNT model is correct, not on those asserting the null hypothesis of no effect at low doses*. These arguments inappropriately shift the burden of proof to proving that LNT is not valid, which is an impossible task.[23] It can always be argued that an LNT-predicted risk might exist but is too small to be detected, rendering the LNT hypothesis unfalsifiable. To be scientifically sound, compelling evidence must be provided that the valid null (no effect at low doses) should be rejected in favor of an alternative hypothesis (eg, there are detrimental health effects at low doses, as predicted by the LNT model; or there are no detrimental health effects at low doses but there are effects at higher doses, as predicted by the threshold model; or there are beneficial health effects at low doses, as predicted by the hormesis model). The current USEPA policy takes the position that the LNT model is accurate unless "compelling evidence to the contrary" is presented. This approach is included in the agency's guidelines that direct the use of the LNT even if the scientific evidence cannot substantiate that conclusion. This is a circular argument that excludes the option of other alternative models from being considered.

USEPA goes on to comment,

> Biophysical calculations and experiments demonstrate that a single track of ionizing radiation passing through a cell produces complex damage sites in DNA, unique to radiation, the repair of which is error-prone. Thus, no threshold for radiation-induced mutations is expected, and, indeed, none has been observed.[10]

This statement relies on a biological plausibility argument to support the use of the LNT dose–response model in LDDR environments. However, a biologically plausible argument based on more recent scientific evidence suggests that extensive protective biological processes are initiated upon initial DNA damage to prevent potential development of cancer (eg, cellular- and tissue-level defense mechanisms including not only DNA damage repair but also apoptosis, premature terminal differentiation, and immunosurveillance[9,24,25]). As explicitly acknowledged by the National Council on Radiation Protection and Measurements (NCRP) over 15 years ago,[26]

> Application of this [microdosimetric] argument to complex endpoints such as radiation-induced carcinogenesis is, however, more uncertain. *Based on these biophysical considerations about the shape of the dose-response relation for low-dose radiation-induced carcinogenesis, conclusions can be drawn if*: (1) radiogenic cancer induction is causally related to radiation induced damage in a single cell and (2) *the ways in which other cells or cell systems subsequently modify the probability that any given initially radiation-damaged cell becomes the clonal origin of a cancer do not vary with dose in a non-linear fashion*. (emphasis added)

More and more scientific evidence has accumulated in recent years that neither of these underlying assumptions are valid.[24,27] In fact, even references cited by USEPA as supporting this position actually contradict it. For example, Trott and Rosemann stated,

> Since the cell is able to repair a very high level of endogenous DNA damage without frequent mutagenic consequences, a further small increment of such DNA damage from low dose rate irradiation should, equally efficiently, be repaired. Mutation rates will only increase if due to higher dose and dose rate, the capacity for high fidelity DNA repair is exceeded.[28]

And also,

> The mechanism which induces 'radiation-induced genomic instability' appears to involve a non-nuclear target and upregulation of oxidative stress, which also is the main mechanism of metabolic DNA damage. These experimental observations are not compatible with a single hit mechanism which is the basis for the microdosimetric justification of the linear-non threshold dose response hypothesis.[28]

Current evidence demonstrates that biological responses to LDDR radiation are distinct from those occurring at high doses.[21,24,29-33] Similarity of mechanisms is one of the fundamental assumptions underpinning the LNT extrapolation from

high-dose and high-dose rate (HDDR) to LDDR, and there is growing evidence that this assumption is inaccurate.

The USEPA's assertion that no threshold in radiation-induced mutations has been observed is inaccurate. Early data on mutations in fruit flies were very influential in adoption of the LNT model. These data actually indicated a threshold but was misrepresented as supporting the LNT model.[34-36] In similar experiments, more recent studies examining mutations in fruit flies confirm that the dose–response is characterized by a threshold or even hormesis.[37-41] These studies relate to another of Hill's criteria—Experiment which can greatly strengthen the case for causation.[20] However, these studies do not support the LNT model but rather a threshold or hormesis model.

A threshold for radiation-induced mutations has also been observed in mice,[42-46] human-hamster hybrid cells,[47] and human cells.[48] These findings also relate to another of Hill's criteria—Consistency, defined by Hill as generality or repeatability[20]—but here again, they do not support the LNT model; instead, they demonstrate thresholds.

The USEPA's own Scientific Advisory Board (SAB)[49] has cautioned the Agency on taking this position on LNT, stating,

> Radiation-induced genomic instability seems to be one of the early stages in the carcinogenesis process and has been seen both *in vitro* and *in vivo*. *These observations challenge the relative importance that initial mutations play in radiation-induced cancer*,[50]

and further,

> *Genomic instability and the ability to modify responses after the radiation exposure both challenge the linear relationship between initial DNA damage and cancer frequency*. (emphasis added)

The USEPA response suggests that unless cells repair DNA damage with 100% fidelity, the risk of cancer is increased.[5,10] This is not supported by current evidence.[24] DNA repair mechanisms act on both radiation-induced damage and on pre-existing spontaneous background DNA damage resulting from oxygen metabolism and other endogenous sources. If the resulting sum of radiation plus spontaneous DNA damage after radiation exposure is less than the level of damage that existed prior to radiation exposure, it is entirely reasonable and biologically plausible that radiation risks are not increased (consistent with a threshold) or may even be decreased (consistent with hormesis).

Nonetheless, USEPA continued,

> Of all the agents demonstrated to be carcinogenic, the evidence for LNT is particularly strong for ionizing radiation. Within limitations imposed by statistical power, the available (and extensive) epidemiological data are broadly consistent with a linear dose-response for radiation cancer risk at moderate and low doses.[10]

Strength of association is another of Hill's criteria.[20] The USEPA states the evidence is strong and consistent with the LNT response at moderate and low doses. However, radiation in general is a weak carcinogen,[51,52] and the evidence that LDDR radiation exposure in particular increases cancer risk is lacking.[21] In fact, many professional organizations have explicitly warned against estimating risks from low-dose radiation environments due to large uncertainties associated with the epidemiologic data.[53-55] The USEPA's position on this point appears to contradict their own guidance document,[6] which states,

> Generally speaking, epidemiology cannot be used to detect and quantify the carcinogenic effects of radiation at doses below about 100 mGy of low-LET [linear energy transfer] radiation because of limitations on statistical power.[56,57]

Is the USEPA Using the Concept of Collective Dose Appropriately?

International expert advisory bodies have repeatedly cautioned against application of the LNT model to calculate hypothetical risks from LDDR exposures.[53,55] For example, United Nations Scientific Committee on the Effects of ionizing Radiation (UNSCEAR) has stated,

> In general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation. . . . the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels.[53]

Similarly, the ICRP has stated,

> Collective effective dose is an instrument for optimisation, for comparing radiological technologies and protection procedures. Collective effective dose is not intended as a tool for epidemiological studies, and it is inappropriate to use it in risk projections. This is because the assumptions implicit in the calculation of collective effective dose (*e.g.*, when applying the LNT model) conceal large biological and statistical uncertainties. Specifically, the computation of cancer deaths based on collective effective doses involving trivial exposures to large populations is not reasonable and should be avoided. Such computations based on collective effective dose were never intended, are biologically and statistically very uncertain, presuppose a number of caveats that tend not to be repeated when estimates are quoted out of context, and are an incorrect use of this protection quantity.[55]

Despite this guidance, the USEPA develops risk estimation tools based on the LNT model to determine cleanup policies and guidelines for its Comprehensive Environmental

Response, Compensation, and Liability Act (CERCLA) superfund sites. Because they multiply very small doses by large populations to predict excess cancer incidence or mortality, these tools conflict with the scientific guidance provided by other governmental or scientific organizations and professional societies. The impact to the United States is real, resulting in enormous cleanup costs that show no demonstrable benefit to society, creates a social stigma on affected communities, and foments fear among the public, causing unnecessary harm by promoting ill-advised decision-making. The USEPA's estimates of cancer incidence and mortality risks due to low doses of ionizing radiation for US population as well as their advice to the public and tools used to establish cleanup levels are at odds with UNSCEAR's and ICRP's guidance. For example, USEPA states,

> ... overall, if each person in a group of 10,000 people exposed to 1 rem of ionizing radiation, in small doses over a life time, we would expect 5 or 6 more people to die of cancer than would otherwise. In this group of 10,000 people, we can expect about 2,000 to die of cancer from all non-radiation causes. The accumulated exposure to 1 rem of radiation, would increase that number to about 2005 or 2006.[58]

This advice to the public is inconsistent with the intended purpose of effective dose (prospective dose estimation for the purpose of optimization), which is inappropriate for predicting future cancer risk.[59]

Is There Scientific Consensus for Using the LNT Model to Estimate Risk in LDDR Environments?

USEPA's comments on the public petitions to the NRC[7,8] stated,

> *Given the continuing wide consensus on the use of LNT* for regulatory purposes as well as the increasing scientific confirmation of the LNT model, it would be unacceptable to the USEPA to ignore the recommendations of the NAS [US National Academy of Sciences] and other authoritative sources on this issue. The USEPA cannot endorse basing radiation protection on poorly supported and highly speculative proposals for dose thresholds or doubtful notions concerning protective effects from low-level ionizing radiation. Accordingly, we would urge the NRC to deny the petition.[10] (emphasis added)

And similarly,

> Over the last half century, numerous authoritative national and international bodies have convened committees of experts to examine the issue of LNT as a tool for radiation regulation and risk assessment. These include the U.S. National Academy of Sciences (NAS), the National Council on Radiation Protection and Measurements (NCRP), the International Commission on Radiological Protection (ICRP), and the United Nations Scientific Committee on the Effects of ionizing Radiation (UNSCEAR). Again and again, these bodies have endorsed LNT as a reasonable approach to regulating exposures to low dose radiation. One exception was a French National Academy Report, which found low-dose radio biological effects in vitro indicative of nonlinearity in the dose response.[10]

This argument was also repeated in[5]:

> To assist the Agency in its assessment of the health risks from ionizing radiation, EPA has often helped sponsor reports from these organizations, particularly from the NAS 'BEIR Committees'. The risk models and supporting evidence is then reviewed by EPA's Scientific Advisory Board of outside distinguished scientists before becoming final and being implemented. Thus, EPA's estimates of risk to low dose radiation reflect a broad scientific consensus.

In these arguments, the USEPA "appeals to authority,"[23] where the LNT model is asserted to be valid because some authority putatively endorses it. This is an academic point because there is in fact no consensus in favor of the LNT model among individual scientists, professional societies, expert advisory bodies, US regulators, nor even within USEPA itself. As acknowledged earlier, contradictory recommendations were issued by the French National Academies of Science and Medicine,[60] and evidence supporting the French conclusions has grown in the recent years. The French report contradicts the claim of consensus among expert advisory bodies in support of the LNT model.[5,10]

The USEPA's own SAB has expressed caution about applying the LNT at low doses as well. The USEPA has claimed that unfettered application of the LNT,

> ... is the position adopted by the USEPA after review by the Agency's Scientific Advisory Board, an independent group of distinguished outside scientists.[10]

However, the SAB's Radiation Advisory Committee cautioned[49]:

> ... a major issue with the choice of the LNT model is whether it is appropriately applied at low doses.
>
> ... while the RAC endorses USEPA's use of the LNT model, the Agency is advised to continue to monitor the science of the biological mechanisms underlying cancer induction at low doses of ionizing radiation and of their influence on the biophysical models used to estimate the cancer risk in this dose range.
>
> At radiation exposures in the range of natural background, it is difficult to distinguish radiation-induced changes in risk from the baseline. Thus, as a cautionary note, the RAC recommends that the USEPA discuss potential problems associated with the use of LNT dose response model risk estimates in very low dose settings. Currently at these low doses, statistically significant differences between the cancer rates among 'exposed' (defined study populations) and 'non-exposed' (defined comparison populations) are not observed.

> As BEIR VII acknowledges, the epidemiological data below 100 mSv (0.1 Sv) are not sufficient by themselves for risk estimation, and considerable cellular and animal data suggest complexities beyond the application of a simplified DNA damage model which historically has been used as support for an LNT dose-response model.

It is important to note that since the SAB last took up this issue and advised USEPA to explicitly monitor developments on these topics, the NCRP has issued comprehensive reports on uncertainties in the measurement and dosimetry of external radiation,[61] internal radiation dose,[62] and in the estimation of radiation risks.[63]

There is also no consensus among US regulators. The US General Accounting Office (GAO) has on multiple occasions investigated whether or not there is a consensus among USEPA, the NRC, and the Department of Energy (DOE) on approaches to regulating LDDR radiation exposures to the public.[2,64-66] Over 20 years ago, the GAO found,

> the radiation standards that have been developed reflect a lack of overall interagency consensus on how much radiation risk to the public is acceptable

and also,

> Differences in radiation limits and risks, calculation methods, and protective strategies reflect the historical lack of a unified federal framework for protecting the public from radiation exposure.[65]

The situation had not been resolved by 2000, with GAO finding,[2]

> U.S. regulatory standards to protect the public from the potential health risks of nuclear radiation lack a conclusively verified scientific basis, according to a consensus of recognized scientists. In the absence of more conclusive data, scientists have assumed that even the smallest radiation exposure carries a risk. This assumption (called the 'linear, no-threshold hypothesis' or model) extrapolates better-verified high-level radiation effects to lower, less well-verified levels and is the preferred theoretical basis for the current U.S. radiation standards. However, this assumption is controversial among many scientists

and also,

> ... USEPA and NRC have disagreed on exposure limits. Although we recommended as far back as 1994 that the two agencies take the lead in pursuing an interagency consensus on acceptable radiation risks to the public, they continue to disagree on two major regulatory applications: (1) the proposed disposal of high-level nuclear waste in a repository at Yucca Mountain and (2) the cleanup and decommissioning of nuclear facilities.

As recently as 2017, the GAO again recommended the DOE take the lead on reestablishing and coordinating federal research on the topic of low-dose radiation effects.[66]

There is also no consensus in support of the LNT model among relevant professional societies.[54,67-69] Extrapolation of LDDR risks via the LNT model is at odds with the advice of professional societies around the world. For example, the Australasian Radiation Protection Society has stated,

> There is insufficient epidemiological evidence to establish a dose-effect relationship for effective doses of less than a few tens of millisieverts in a year above the background level of exposure and further, ... no inference may be drawn concerning the risk to health or risk of fatality of an individual from an effective dose below 10 mSv in a year. For individual doses less than some tens of millisieverts in a year, risk inferences are unreliable and carry a large uncertainty that includes the possibility of zero risk.[68]

In the United States, the HPS has concluded,

> The Health Physics Society advises against estimating health risks to people from exposures to ionizing radiation that are near or less than natural background levels because statistical uncertainties at these low levels are great ... Substantial and convincing scientific data show evidence of health effects following high-dose exposures (many multiples of natural background). However, below levels of about 100 mSv above background from all sources combined, the observed radiation effects in people are not statistically different from zero. Scientists evaluate and estimate radiation risk using several assumptions that, taken together, may lead to a range of hypothetical health risk estimates for any given exposure scenario. For radiation protection purposes and for setting radiation exposure limits, current standards and practices are based on the questionable premise that any radiation dose, no matter how small, could result in detrimental health effects such as cancer or heritable genetic damage. Implicit in this linear no-threshold (LNT) hypothesis is the core assumption that detrimental effects occur proportionately with radiation dose received (NAS/NRC 2006). However, because of statistical uncertainties in biological response at or near background levels, the LNT hypothesis cannot provide reliable projections of future cancer incidence from low-level radiation exposures (NCRP 2001).[54]

Additional examples from medical physics and radiology professional societies are provided in "What Other Information Is Available in the Scientific Literature and Does It Support the Continued Use of the LNT Model for LDDR Environments?" section.

In addition to expert advisory bodies and professional societies, numerous individual scientists have argued against application of the LNT at low doses.[24,70-72] Studies have also been conducted of individual scientists' views regarding the accuracy of the LNT dose–response model for radiation effects[73,74] (Table 1). A survey of scientists employed at US national laboratories revealed that 70% believed that a threshold model

Table 1. Survey of Scientists Regarding the Most Accurate Radiation Dose–Response Model for Cancer.[73,74]

Surveys	Respondents	Percent Supporting LNT Model	Percent Supporting Threshold Model	Other
United States	National Labs	12	70	18[a]
	Union of Concerned Scientists	21	48	31[a]
Subscribers to *Science*	United States	19	75	6[b]
	Britain	21	71	8[b]
	France	18	70	13[b]
	Germany	22	64	13[b]
	Other European Union	23	69	8[b]

Abbreviation: LNT, linear no-threshold.
[a]The "other" category includes "supralinear" and "don't know" responses.
[b]The "other" category includes "supralinear" responses.

accurately reflected radiation effects, compared to only 12% who believed an LNT model is accurate.[74] Even among members of the Union of Concerned Scientists, a group that has expressed concerns about the US nuclear power industry, 48% believed a threshold model accurately describes LDDR effects while only 21% favored an LNT model. The results were similar when scientists from the United States and Europe who subscribe to the journal *Science* were surveyed[73]: (1) 75% of US scientists believed a sublinear threshold model accurately described radiation effects, compared to only 19% who favored an LNT model; (2) for British scientists, the breakdown was 71% for sublinear threshold and 21% for LNT models; (3) for French scientists, 70% and 18%, respectively; (4) for German scientists, 64% and 22%, respectively, and (5) for other European scientists, 69% and 23%, respectively. These studies indicate that a majority of individual scientists are skeptical of the accuracy of the LNT model—exactly the opposite of a pro-LNT consensus claimed by USEPA.[5,10]

Should the BEIR VII Report Continue to be Used to Justify the Use of the LNT Model for LDDR Radiation Environments?

In short, the answer is "no." The USEPA places great weight on a few scientific references to support its application of the LNT model, most notably, the BEIR VII report from the US NAS.[6] For example, USEPA states,

> The BEIR VII study, which was sponsored by several federal agencies including the USEPA and the NRC, determined that 'the balance of evidence from epidemiologic, animal and mechanistic studies tend to favor a simple proportionate relationship at low doses between radiation dose and cancer risk.'[10]

The NAS originally adopted the LNT model as the basis for its philosophy to protect against radiation-induced genetic mutations in the human population at the recommendation of its Biological Effects of Atomic Radiation Committee Genetics Panel in 1956.[75] This recommendation was made in spite of the fact that radiation-induced genetic effects in the offspring of irradiated parents have never been observed in humans. Recent historical research has revealed that this recommendation was made under questionable circumstances ([76-80] but see also[81-83]). Even so, the LNT model was later expanded and applied to radiation-induced cancer risks. Controversial from the beginning, this recommendation nevertheless initiated decades of institutional inertia, with multiple iterations of NAS Committees repeatedly reaffirming the suitability of the LNT model as the basis of radiation protection philosophy, most recently in the BIER VII report over a decade ago.[4] The BEIR VII Committee concluded,

> . . . current scientific evidence is consistent with the hypothesis that there is a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans.

Although they acknowledged that a linear-quadratic model fit the data better than the LNT model at low doses, they reported the improvement was not statistically significant. In large part, because the NAS inappropriately treated the LNT model as if it were the null hypothesis rather than appropriately treating it as an alternative hypothesis to be tested against the null of no effect, the LNT model became the Committee's preferred recommendation. In turn, the USEPA incorporated BEIR VII risk models into their policy and guidance.[84]

However, two major pieces of evidence the BEIR VII Committee relied upon to support their endorsement of the use of the LNT model to estimate risks from low doses, the Lifespan Study (LSS) of the Japanese atomic bomb survivors and the 15-country study of nuclear workers, no longer support the LNT model.[85] We summarize the problems with continuing to cite these two pieces of evidence to justify risk estimates using the LNT model in LDDR environments below.

It is widely acknowledged (in the BEIR VII report and elsewhere) that the LSS was the most influential study in setting radiation protection guidelines around the world. It is also evident that even these data set do not provide definitive evidence of increased cancer risk after exposure to low radiation doses.[86] In fact, the most recent epidemiological study on cancer mortality in the Japanese survivors of the atomic bombings states,

> the estimated lowest dose range with a significant ERR [excess relative risk] for all solid cancer was 0 to 0.20 Gy.[87]

Another way of saying this is that no significant ERR was observed for doses below 0.20 Gy. The authors also concluded that,

> . . . statistically significant upward curvature was observed when the dose range was limited to 0–2 Gy . . . The curvature over the 0–2 Gy range has become stronger over time.

This means the argument for an LNT relationship has weakened over time. This is an example of epidemiological data possibly reflecting dissimilarity of biological responses to LDDR and HDDR; however, it is not discussed by the authors in spite of explicit calls to integrate biology and epidemiology.[88,89] Despite that evidence, these authors concluded,

> . . . a formal dose-threshold analysis indicated no threshold; *i.e.* zero dose was the best estimate of the threshold.[87,90]

Reviewing their threshold analysis, others found that they excluded the possibility of negative risk values despite eight of the 10 lowest data points having confidence intervals, including negative values. Alternative analyses that did not exclude negative values revealed the possibility of a nonzero threshold.[35,91-94]

Similarly, for cancer incidence in the LSS cohort,

> The lowest dose range that showed a statistically significant dose response using the sex averaged, linear ERR model was 0–100 mGy.[95]

In other words, there are no detectable health effects below 100 mGy. It is evident that statistical power limitations preclude the selection of one alternative hypothesis over another (eg, LNT vs linear with threshold); therefore, the assertion that the LSS data provide definitive evidence in support of the LNT is not accurate. A threshold model is also consistent with both the latest solid cancer incidence and the mortality data.

The second piece of evidence the BEIR VII Committee relied heavily upon was the so-called "15-country study."[96] This study initially concluded that,

> Significantly increased risks were found for mortality from all cancers excluding leukemia and from lung cancers.

However, further analysis revealed that this conclusion is also no longer valid. The Canadian Nuclear Safety Commission concluded that Atomic Energy of Canada, Ltd nuclear energy workers cohort included in the original 15-country study did,

> . . . not have an increased risk of solid cancer mortality. Incomplete dose records are likely the cause for the apparent increased risk of solid cancer mortality in AECL NEWs first employed before 1965 (1956-1964).[97]

Furthermore, Zablotska et al[98] concluded:

> Significantly increased risks for early AECL workers are most likely due to incomplete transfer of AECL dose records to the National Dose Registry. Analyses of the remainder of the Canadian nuclear workers (93.2%) provided no evidence of increased risk

and,

> Study findings suggest that the revised Canadian cohort, with the exclusion of early AECL workers, would likely have an important effect on the 15-country pooled risk estimate of radiation-related risks of all cancer excluding leukaemia by substantially reducing the size of the point estimate and its significance.

These findings should serve as a warning against relying on BEIR VII to justify the use of the LNT model for LDDR risk estimation purposes.

In summary, two influential pieces of evidence relied upon by the BEIR VII Committee (the LSS cohort and the 15-country study) no longer support the LNT model based on the latest scientific literature. However, the USEPA relies heavily upon the recommendations of the BEIR VII report on this issue and continues to use it to support is current policies and risk assessment strategies. This evidence alone is enough to warrant a new look at the science for risk assessment decision-making and determining radiation cleanup levels in LDDR environments.

What Other Information is Available in the Scientific Literature and Does it Support the Continued Use of the LNT Model for LDDR Environments?

The USEPA has cited studies published after BEIR VII, which they assert provides support for the LNT model in LDDR environments[99]:

> Since publication of BEIR VII, additional evidence has accumulated supporting the use of LNT to extrapolate risk estimates from high acute doses to lower doses and dose rates. In this connection, we would note, inter alia, results of epidemiological studies on: nuclear workers in the United States, France and the United Kingdom[100]; residents along the Techa River in Russia who were exposed to radionuclides from the Mayak Plutonium Production Plant[101,102]; and children who had received CT scans.[103] These studies have shown increased risks of leukemia and other cancers at doses and dose rates below those which LNT skeptics have maintained are harmless - or even beneficial.[10]

Follow-up studies of a selected part of the cohort included in the 15-country study has recently been published to examine leukemia[100] and solid cancer[104] risks. These studies, also known as the International Nuclear Workers Study (INWORKS)] studies, examined risk in worker cohorts from the United States, France, and the United Kingdom (a subset of the larger cohort included in the 15-country study). The leukemia study[100] concluded,

> This study provides strong evidence of positive associations between protracted low-dose radiation exposure and leukaemia.

Similarly, the solid cancer study[104] concluded,

> The study provides a direct estimate of the association between protracted low dose exposure to ionising radiation and solid cancer mortality.

Several methodological questions have been raised about these studies,[105,106] and the authors have replied.[107] In addition, numerous methodological objections have been raised in Sacks et al.[108] These include:

1. failure to account for natural background radiation exposure, the differences in which potentially dwarf the occupational exposures of the study cohort;
2. failure to account for medical exposures experienced by the public;
3. failure to account for dose–rate effects;
4. the a priori assumption of an LNT dose response;
5. mischaracterization of the *y*-intercept as 0 total dose when in fact it was 0 occupational dose;
6. arbitrary exclusion of all dose responses except LNT and linear-quadratic (which actually provided a better fit to their observed data, but the authors claimed the improvement was not statistically significant);
7. dismissing 6 of 7 disease outcomes as being highly imprecise rather than stating that they are not statistically significantly different from no-effect;
8. creating an artificial disease category by arbitrarily combining 3 forms of leukemia and excluding a fourth, then characterizing this artificial grouping as an additional statistically significant association;
9. providing misleading characterizations of the data above 200 mGy as statistically significant when in fact, only the 200 to 300 mGy dose category was significantly elevated, whereas the highest dose category was not (nor was any other dose category);
10. insufficient consideration of age as a possible confounder;
11. a priori and arbitrary consideration only of the possibility of increased risks and excluding the possibility of decreased risks; and
12. the arbitrary choice of a 90% confidence limit rather than the more conventional 95%, thus increasing the possibility of significance, then mischaracterizing the results as strong evidence of risk from LDDR radiation exposure.

To this list of methodological shortcomings, we add the omission of *occupationally required* medical imaging examinations (which are distinct from medical doses received by the public at large—raised as #2 above), resulting in potential significant underestimation of external radiation dose. With regard to potential confounding by diagnostic medical dose, the INWORKS authors state,

> ... for confounding to occur, medical radiation exposures would need to be associated with occupational doses ... which is unlikely to be the case.[107]

The basis for the authors' conclusion that such confounding is unlikely is not provided. The omission of dose from medical imaging received by workers as a condition of employment presents one of the most serious questions about the methodology of these studies, as it likely resulted in potentially significant underestimation of external radiation dose. At several of the US sites included in the study, workers were required to undergo a medical examination at least yearly, which included medical imaging examinations. Of particular concern is the use of photofluorography in the early years (eg, 1940s to 1950s). Photofluorography delivered high-dose rate radiation exposures to workers at the Savannah River Site (1951-1960, 0.46 mGy per examination to male red bone marrow),[109] Hanford (1943-1962, 1.41 mGy),[109] and the 3 Oak Ridge Sites: Y-12 (at least 1943-1947, 2.76 mGy),[110] X-10 (at least prior to 1947, 2.58 mGy),[111] and K-25 (1945-1956, 2.0 mGy).[112] So, for example, a worker at Hanford from 1943 to 1962 could have received a red bone marrow dose of ~27 mGy from photofluorography alone. Although these are not especially large doses, the authors reported recorded mean occupational external bone marrow doses of only 16 mGy and median doses of only 2.1 mGy, and they claim to have observed increased leukemia risks. If that is true, then even larger potential doses from occupationally required medical examinations cannot be casually dismissed. The impact of medical imaging examinations workers received as a condition of employment has been specifically studied at one of the sites included in the INWORKS study.[113,114] Work-related medical imaging examinations were the predominant source of radiation exposure among workers at the K-25 site. In fact, the work-related medical imaging dose was on average 50 times higher than the recorded occupational dose.[113] Occupationally required medical imaging could certainly influence the estimation of possible thresholds (which the authors of the INWORKS studies did not report), estimates of risk per unit dose, and the shape of the dose–response relationship.[113] Furthermore, at some sites, workers judged to be at high risk (eg, those performing jobs where they received higher occupational radiation dose) were examined more frequently, indicating nonrandom distribution of medical radiation exposure among the cohort and subsequent bias. Neglecting this important source of exposure seriously compromises the conclusions of the INWORKS study. At least for the US sites, workers' medical records are available, so including this dose should be feasible. The importance of this issue for the UK and French cohorts included in the INWORKS study should also be examined.

For the Techa River cohort, it is unclear why USEPA chose to cite an outdated reference[101] when there is a more recent update[115]; however, risk estimates in the most recent update are less than half of the estimates in the earlier reference USEPA cited. Furthermore, Krestinina et al[115] states,

> For the basic dose–response model, the ERR was assumed to be linear in dose but we also considered models where the dose response was taken as a linear-quadratic, a pure quadratic function of dose, or threshold models in which the ERR was assumed to be 0 up to some threshold dose and taken as linear for higher doses.

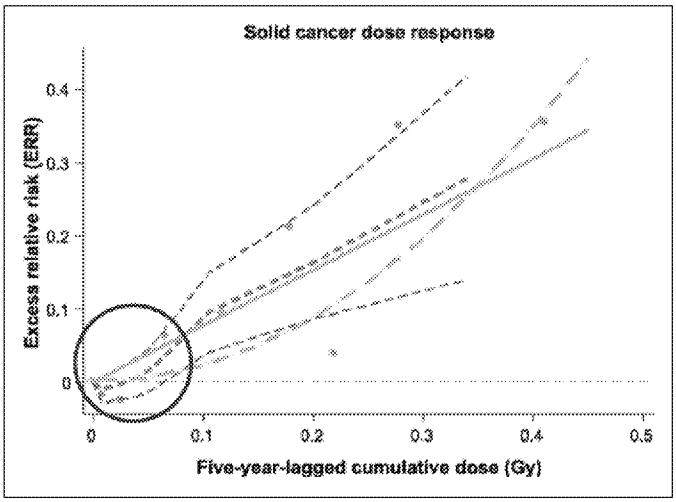

Figure 1. Solid cancer excess relative risk (ERR) estimates for the Techa River cohort plotted against stomach dose. Reproduced from figure 1 of Davis et al[102], used with permission, circle added for emphasis.

No further details are provided on their analysis of thresholds. It is not clear whether the authors allowed ERR to assume negative values, which would certainly be indicated given that the total leukemia rates reported for the 5 lowest dose groups were lower than the control group (those who received <0.01 Gy). Only the 2 highest dose groups (those receiving 0.5-1 Gy and 1+ Gy) exceeded controls. For leukemia excluding chronic lymphocytic leukemia, the rates for 2 of the 3 lowest dose groups were below that for the control group, suggesting a threshold or even potential hormetic effect which is often dismissed as a potential healthy worker effect. The authors reported that their data, "... are consistent with a linear dose response ..."; however, they do not report whether or not their data are also consistent with a threshold or hormetic dose response, which would seem to be the case given these results. If multiple models adequately describe the observed dose response, then USEPA should not cite these results as supporting the LNT model and excluding the threshold model as petitioned by SARI.

For solid cancers in the Techa River Cohort, the situation is similar. The USEPA cited,[102] and again, the authors claimed,

> There is a statistically significant ($P = 0.02$) linear trend in the smoking-adjusted all-solid cancer incidence risks.

However, a closer look at the data in this study reveals that the two lowest dose categories have ERR estimates lower than the zero dose controls, consistent with a hormetic dose response or at least a threshold (Figure 1). This is another example of epidemiological data possibly reflecting the dissimilarity of biological responses to LDDR and HDDR, but again it is not discussed by the authors.

Within the past few years, new studies of pediatric patients receiving computed tomography (CT) medical imaging examinations claimed to observe increases in risks from relatively low doses (though delivered at a high-dose rate).[103,116] These studies received extensive press coverage, and almost immediately, claims were made that,

> ... the new data confirm that the cancer risk associated with the radiation from a CT scan is very small, but not zero.[117]

In presentations to the Interagency Steering Committee on Radiation Standards, USEPA has referenced these studies to suggest potential adverse health effects from LDDR radiation.[99] However, these early enthusiastic pronouncements have not held up to scientific scrutiny. A number of significant methodological issues have been identified in these studies,[118,119] including (1) individual doses were not directly assessed, but rather "typical" doses were assumed; (2) doses applied were for adults and assumed no decrease for pediatric patients, even though this is the standard of care; and (3) the reason for the CT was not considered, and it is possible that the underlying condition indicating the CT has associated cancer susceptibility (this point was acknowledged in one of the USEPA presentations[99,120]). On the latter point, as explained by Ulsh,[91]

> One of the strongest associations[103] observed was for gliomas, but they did not control for prior head injury. Head injuries are a common reason for head CT in children, and head injury may be associated with brain tumors.

This assessment agrees with UNSCEAR,[121] which concluded

> ... There are concerns about the risk estimates because of lack of information about indications for the CT scans and the consequent potential for 'reverse causation' (*i.e.*, cancers may have been caused by the medical conditions prompting the CT scans rather than by the CT dose).

The NCRP came to similar conclusions, stating:

> Children who receive frequent examinations may have some underlying disability related to the outcome of interest. That is, a child who receives multiple CT examinations of the head may have a central nervous system disorder that is prompting such examinations and it is these underlying disorders that are related to the cancer diagnosis and not the CT radiation dose.[63]

Furthermore, two recent studies from France[122] and Germany[123] have demonstrated that failing to account for the underlying reason requiring the examination can inflate risk estimates in studies of populations exposed to CT scans.

In spite of the UNSCEAR and NCRP conclusions, and multiple papers pointing out the limitations of these studies (eg,[91,119]), they continue to be cited by USEPA and others as providing strong or definitive evidence of risks of very low radiation doses and supportive of the LNT model.[99] However, the application of the LNT model and the As Low As Reasonably Achievable (ALARA) principle to medical imaging has come under heavy criticism.[72,124-126] Professional societies

with expertise in medical imaging continue to unanimously maintain that the carcinogenicity of low radiation doses has not been demonstrated, and estimates of risks from low doses like those associated with medical imaging examinations remain speculative and unproven. For example:

- American Association of Physicists in Medicine

  At the present time, there is no convincing epidemiological evidence of increased cancer incidence or mortality from low radiation doses (<100 mSv). Because medical imaging exposures are typically much lower than 100 mSv, when such exposures are medically appropriate, the anticipated benefits to the patient are highly likely to outweigh any small potential risks. Therefore, when discussions of risk occur, it is essential that the benefit of the clinical task also be discussed. Additionally, the AAPM discourages describing potential risks associated with medical imaging using predictions of hypothetical cancer incidence and deaths. These predictions are contrary to directives of radiation protection organizations, are highly speculative and can lead to sensationalistic coverage in the public media, leading some patients to fear or refuse appropriate medical imaging.[69]

- International Organization for Medical Physics

  Prospective estimates of cancers and cancer deaths induced by medical radiation should include a statement that the estimates are highly speculative because of various random and systematic uncertainties embedded in them. These uncertainties include dosimetric uncertainties; epidemiological and methodological uncertainties; uncertainties from low statistical power and precision in epidemiology studies of radiation risk; uncertainties in modeling radiation risk data; generalization of risk estimates across different populations; and reliance of epidemiological studies on observational rather than experimental data. Such uncertainties cause predictions of radiation-induced cancers and cancer deaths to be susceptible to biases and confounding influences that are unidentifiable.[127]

- The Society for Pediatric Radiology

  To prevent misconceptions and public alarm, it is important to realize that the radiation used in CT scans has not been proven to cause cancer during a child's lifetime. The very small risk of cancer from radiation exposure is an estimate and is based on information and statistics that are debatable.[67]

USEPA has also cited studies of natural background and other environmental LDDR radiation exposures. Studies to understand health effects on people exposed to LDDR radiation are especially important, since they more closely reflect the environment following a radiological cleanup effort. They also serve to help the agency determine whether the cleanup policies are adequate to protect human health and environment while accounting for social and economic factors (ie, do they do more good than harm to society?). USEPA cited a study of leukemia risk due to natural background radiation exposure[128] and noted that this study claimed to have observed significant excess risk associated with dose rates as low as 1 mGy/yr.[99] We reviewed[128] and have identified several methodological issues.

The authors conclude,

> The possibility of confounding by some unidentified factor can never be entirely disproved, and is of particular concern when dealing, as here, with small RRs. However, we were unable to identify any mechanism whereby such confounding might plausibly account for the observed magnitude and specificity of effect in this study.

Socioeconomic status was the only confounder considered. There is evidence that paternal smoking is also associated with increased risk of childhood leukemia,[129] yet the authors did not consider this. The USEPA presented[128] as evidence of an LNT relationship for LDDR exposures despite the fact that it ignored potential confounding due to exposure to tobacco smoke. It is also worth noting that USEPA explicitly criticized other ecological LDDR studies that contradicted the LNT model[130,131] for not accounting for smoking ([132,133] but see also[134,135]). In the same presentation citing,[128] USEPA acknowledged the potential role of confounding factors, stating "variations in cancer rates due to other causes tend to swamp out those due to [ionizing radiation] exposure," but apparently did not consider the potential for smoking to confound this study by noting this limitation.

This study[128] estimated background gamma and radon doses based on the residence location of the mother, using county measurements. This information was available for cases both at birth and at time of diagnosis. It was discovered that about half of the cases had moved between birth and diagnosis. For controls, only the residence location at time of birth was available, so the number of the controls who moved after birth is unknown. The UNSCEAR warned that,

> The study should be interpreted with caution because of the large uncertainties associated with using an ecological measure of dose.[121]

The study considers only radiation exposure from natural background gamma radiation and radon. It ignores other, potentially larger sources of radiation exposure, for example, medical exposure. This is in spite of the fact that one of the coauthors of this study (MPL) was a coauthor of a separate study which claimed that exposure of British children to CT scans has increased their leukemia risk.[103] If it is true that exposure to CT scans is an important risk factor for childhood leukemia in this population, then omitting it from Kendall et al[128] cannot be justified. This is not consistent with the author's stated inability to identify other possible sources of bias or confounding.

The number of cases with a γ-ray dose rate different from their control(s) was 14 308 (52% of all cases). This means that for 48% of the cases, the γ-ray dose rate was not different from their controls. This is not a result that strongly demonstrates a causal relationship between background γ-ray dose rate and

leukemia. This observation does not satisfy Hill's criteria of strength of association.[20]

The authors used a log-linear logistic model for data analysis. But the use of such a model to analyze dose–risk relationships contains the intrinsic assumption that dose is linearly related to leukemia risk without threshold. They did not report testing other possible dose–response relationships. The authors assumed the validity of the LNT model, and citing this study in support of the LNT model is therefore a circular argument.[23]

We also note that the USEPA presentations do not discuss the numerous studies of high natural radiation background areas that have observed no excess risks of cancer, even in populations exposed to dose rates well in excess of 100 mGy/yr (eg, [136-141]), except to categorically characterize them as "specious." An objective evaluation of these studies is warranted to better understand any health effects from LDDR exposure to ionizing radiation, especially following the large-scale accidents in Chernobyl and Fukushima.

A similar LDDR situation, but involving a man-made elevated radiation background, occurred in Taipei, Taiwan, where construction materials contaminated with ^{60}Cobalt were used to build hundreds of structures throughout the city.[142] These buildings included schools and nearly 1000 apartments. More than 4000 people were chronically exposed to elevated radiation levels in this incident, some estimated as high as 1.2 Gy of cumulative dose.[143] It has also been the basis of legal action against the Taiwanese government.[144] The USEPA cited a study of this population as supporting the LNT model.

Doses to the apartment dwellers were estimated by survey instrument measurements in the affected apartments and compared to doses measured by personal dosimeters.[145] This study found agreement to within 10% to 15% for adults but only to within 60% for children. Large uncertainties were also noted in other dose reconstruction efforts,[146] which found that children received the smallest radiation doses compared to other family members. Reconstructed doses were found to agree with measured doses to within a factor of 3.[147] Radiation doses have also been measured using thermoluminescent dosimeters (TLDs),[148] and studies have been conducted to determine how to convert TLD measurements to doses received by residents using phantoms.[149]

Epidemiological studies of this population reveal evidence that low doses of radiation not only failed to increase cancer risk but actually are consistent with a protective effect.[150] A study of cancer mortality in this population observed,

> The experience of these 10,000 persons suggests that long term exposure to radiation, at a dose rate of the order of 50 mSv (5 rem) per year, greatly reduces cancer mortality . . . .[151]

A separate study of cancer incidence was also conducted.[152] The abstract of this article highlighted the few specific cancer subtypes that yielded increased standardized incidence ratios (SIRs) based on very low numbers of cases (eg, leukemia, 7 cases vs 3.3 expected). No mention was made in the abstract of the lack of increase for the other 19 types of cancer which showed no statistically increased risks, nor more importantly, the observation of statistically significantly lower SIRs for all cancers (95 observed vs 114.9 expected), all cancers except leukemia (88 observed vs 111.6 expected) and all solid cancers (82 observed vs 109.5 expected). The USEPA's presentation highlighted only the result for leukemia and breast cancer from a follow-up study that arbitrarily excluded the possibility of lower risks in the exposed population and forced a linear fit to the data on selected cancers to estimate hazard ratios at 100 mGy.[153] The hazard ratio at 100 mGy for leukemia excluding chronic lymphocytic leukemia was just barely significant at the 90% α level (confidence interval [CI], 1.01-1.31) but not at the more conventional 95% level. The USEPA presentations did not discuss that no statistically significant increases were observed in all cancers, all cancers excluding leukemia, all solid cancers, or cancers of the cervix, lung, thyroid, liver, stomach, or rectum, even when the data were forced to follow an LNT model. Further, the USEPA presentation did not mention two other studies, including a larger study of cancer incidence by the same authors, which found statistically significantly *reduced* mortality[151] and incidence[152] of all cancers combined and all solid cancers, suggesting not only a lack of cancer risk from low radiation doses but possibly also a protective effect. This creates the misleading impression that the Taiwan studies support the LNT model when in fact they directly contradict it.

Another update on this cohort was recently published,[154] which claimed,

> Dose-dependent risks were statistically significantly increased for leukaemia excluding chronic lymphocytic leukaemia (HR [hazard ratio] 100 mSv 1.18; 90% CI 1.04-1.28), breast cancers (HR100 mSv 1.11; 90% CI 1.05-1.20), and all cancers (HR 100 mSv 1.05; 90% CI 1.0-1.08, $P = 0.04$).

However, as observed by Doss,[155]

> The Hsieh et al publication reports that 249 cancer cases were observed in the cohort up to the end of 2012. To calculate the SIR, we need to know the expected number of cancer cases for the same period. In the 2006 report, Hwang et al reported that the expected number of all cancers was 114.9, and the average age of the irradiated cohort was 33.3 at the end of 2002 (The average age of the population was 17.1 at the time of irradiation and the cohort was followed-up for an average of 16.2 years).[152] Hence, for the Hsieh et al publication, the average age at the end of the study period (end of 2012) would be 43.3. The cancer incidence rates for the ages of 33.3 and 43.3, obtained by interpolation of the average of male and female cancer incidence rates during 1998–2002 from Taiwan Cancer Registry (TCR, 2008), are 86.3 and 222.4, respectively, indicating there would be an increase in cancer incidence between these two ages by a factor of ~2.58. Therefore, considering the 114.9 expected cases to the end of 2002 (Hwang et al, 2006), the expected cancer cases up to the end of 2012 would be 296.4, resulting in a SIR of 249/296.4.0.84 (95% CI: 0.74–0.95). ***Thus, the reduction of cancer rate in the irradiated cohort is***

> ***significant in the updated data also***. A similar analysis of the data published in 2008[153] shows that SIR for that study would be 0.75 (95% CI: 0.61–0.88), based on 117 observed and 156.8 expected cancers to the end of 2005, again indicating reduction of all cancers in the irradiated cohort. ***Hsieh et al have failed to discuss the significant reduction of overall cancers in the irradiated cohort***. (emphasis added)

Is it Appropriate to Regulate Ionizing Radiation in the Same Manner as Toxic Chemicals?

In 1992, the USEPA SAB provided guidance on ways to harmonize risk assessment and risk-reduction strategies for radiation and chemicals.[156] They noted that the regulations for radiation and chemical risks developed under different paradigms and stated:

> USEPA's priorities should be directed towards reducing the greatest risks first, especially when that can be accomplished economically. The corollary to that principle is that similar risks should be treated similarly, which calls for harmonization, in so far as is possible, of risk reduction strategies between chemical and radiation. *Harmonization does not necessarily imply identical treatment, but it does imply that any differences in treatment are clearly explained and justified*. (emphasis added)

The options noted in the SAB Commentary were:

1. bring risk-reduction strategies for excess radiation exposures consistently in line with the chemical paradigm, a direction that it noted that some parts of the agency were already headed;
2. bring chemical risk-reduction strategies more in line with the radiation paradigm; or
3. achieve harmony between the 2 systems by modifying both in appropriate ways, explaining residual differences, and placing more emphasis on what can reasonably be achieved. In this case, background risk could be incorporated, and the balancing of benefits and costs of risk-reduction measures could be strengthened while maintaining much of the Agency's current approach to chemicals.

The radiation paradigm approach to control radiation exposures is based on principles developed over many decades by the ICRP and the NCRP.[75] These principles are:

1. JUSTIFICATION: the need to justify any radiation exposure on the basis that the benefits to society exceed the overall societal cost;
2. ALARA (Optimization): maintain any exposures as low as reasonably achievable, economic and social factors being taken into account; and
3. LIMITATION: radiation exposures are kept to levels of *acceptable risk*.

As described by the ICRP,

> For any situation where intervention is considered, some protective actions might be justified while others are not justified. Of those protective actions which are justified, it is necessary to establish the level at which the best protection will be provided. In other words the radiation detriment averted by each protective action should be balanced against the cost and other detriments of the action in such a way that the net benefit achieved by the protective action is maximized (*i.e.* optimization of protection).[157]

The principles of ALARA (Optimization) and LIMITATION can be viewed as a "top-down" approach to limit radiation exposure and health risk (Figure 2). Therefore, radiation exposures are considered acceptable if they are less than a specific limit and they are as low as reasonably achievable. Compliance with a dose limit alone does not define acceptable exposures or risk.

The chemical paradigm approach can be viewed as a "bottom-up" approach. The historical use of this paradigm by the USEPA is based on the Delaney Clause of the Federal Food, Drug and Cosmetic Act Food Additives Amendment of 1958. This clause set a standard of *zero* risk to the public from carcinogenic food additives (eg, pesticides) that concentrate in processed foods. This was interpreted in terms of a "negligible" but nonzero lifetime cancer risk of 10^{-8}, which was later increased to 10^{-6} due to pesticide measurement difficulties at levels corresponding to the lower risk. This lifetime cancer risk criterion and the concept of risk goals were later incorporated into various USEPA regulations (eg, CERCLA, Safe Drinking Water Act, Clean Air Act, and Resource Conservation and Recovery Act). This paradigm has two basic elements:

1. a goal for acceptable risk and
2. allowance for an increase (relaxation) in risks above the goal, based primarily on considerations of technical feasibility and cost.

The USEPA made the decision to regulate radiation the same way it regulates toxic chemicals for consistency purposes,[158] despite advice from the SAB describing problems with such an approach[159]:

> To many radiation scientists, reducing excess exposures much below 100 mrem/yr seems unnecessary and in any case exceedingly difficult to monitor for compliance because it is within the natural variability of background.
>
> The application of standard chemical risk-reduction criteria to radionuclides in these situations leads to limitations on excess radiation dose that are small in comparison to natural background radiation.
>
> "In calculating excess risk from human sources of a chemical, background levels, if any, are therefore frequently seen as irrelevant . . . ." This is in marked contrast to radiation, which is universally distributed in the natural environment.

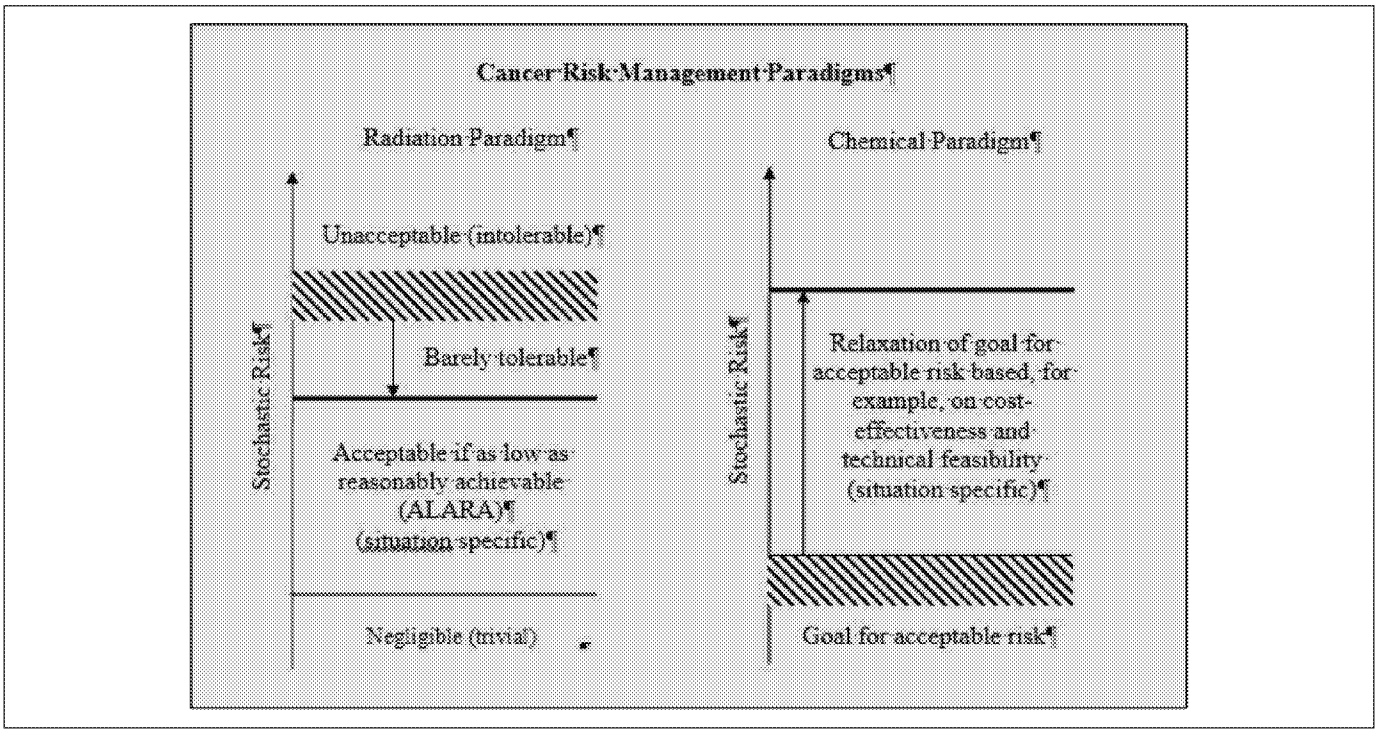

Figure 2. Cancer risk management paradigms. Reprinted with permission from the National Council on Radiation Protection and Measurements, http://NCRPonline.org.

The USEPA treats inorganic metals differently than other chemicals. In the assessment of human risks from exposures to inorganic metals,[160] USEPA takes into account metals that are naturally occurring and vary in concentrations across geographic regions. According to USEPA, the implications of these properties include:

> Humans, other animals, and plants have evolved in the presence of metals and are adapted to various levels of metals. Many animals and plants exhibit geographic distributions that reflect variable requirements for and/or tolerance to certain metals. These regional differences in requirements and tolerances should be kept in mind when conducting toxicity tests, evaluating risks, and extrapolating across regions that differ naturally in metals levels.

The USEPA also acknowledges that some metals are essential for maintaining proper health of humans, animals, plants, and microorganisms. As a result, USEPA considers the following implications for risk assessment[160]:

> Adverse nutritional effects can occur if essential metals are not available in sufficient amounts. Nutritional deficits can be inherently adverse and can increase the vulnerability of humans and other organisms to other stressors, including those associated with other metals.
>
> Excess amounts of essential metals can result in adverse effects if they overwhelm an organism's homeostatic mechanisms. Such homeostatic controls do not apply at the point of contact between the organism and the environmental exposure. Essentiality thus should be viewed as part of the overall dose-response relationship for those metals shown to be essential, and the shape of this relationship can vary among organisms. For a given population, 'reference doses' designed to protect from toxicity of excess should not be set below doses identified as essential. Essential doses are typically life-stage and gender specific.

These properties are analogous to those ascribed to radiation by the threshold and hormesis response models. An exception has been made to treat risk assessment for inorganic metals differently because of their essential characteristics or natural existence in background. Radiation has not been afforded the same consideration despite the similarities with inorganic metals. Instead, USEPA has stated,

> . . . as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial *may not be mentioned*.[161] (emphasis added)

and further,

> As a general principle, our practice is not to base risk assessments on adaptive, non-adverse, or beneficial events.[161]

Applying this guidance to radiation risk assessment excludes any scientific evidence on potential benefits from radiation exposures simply by policy mandate. That introduces bias by allowing only information claiming support for the LNT model

while prohibiting evidence that contradicts it. Excluding evidence of adaption or benefits, and only considering evidence of harm, is contrary to radiation protection philosophy as described by the ICRP.[162] National and international expert advisory bodies acknowledge adaptive and hormetic effects, and their consideration has even been formally included in new European standards for protection of the environment against radiation.[163]

Regulating radiation the same way as toxic chemicals also does not take into account that risks from radiation exposure have been established based largely on observations in humans exposed to well-known individual doses, whereas chemical risks are more often based on projections from experiments on animals or human epidemiology that suffer from poorly characterized individual exposures. Since background radiation is an underlying factor that isn't present for most toxic chemicals, the USEPA SAB acknowledged the existence of threshold models for radiation carcinogenesis (eg, the radium dial painters) or at least "practical thresholds" (eg, the idea that cancer latency was inversely related to dose such that manifestation of risks at low doses could be delayed so long that no cancers would occur during a normal lifetime).[156]

Radiation protection philosophy is distinct from toxic chemical protection philosophy:

> The precautionary principle is an alternative risk management strategy that gives disproportionate weighting to technological risks. It is often summarized by the phrase 'better safe than sorry' and requires forgoing, postponing or otherwise limiting a product or activity until uncertainty about potential risks has been resolved in favor of safety. ALARA, on the other hand, treats risks and benefits on a level playing field. Accordingly there is no prescribed dose goal. The end result of an ALARA practice is a residual dose and risk that is considered acceptable.[164]

The distinguishing hallmark of the ALARA philosophy is that interventions and radiation protection policies must be low, reasonable, and achievable. The USEPA application of the LNT model for determining risk and developing cleanup levels often result in very low numbers that are nearly three orders of magnitude below, where adverse effects are reliably observed and significantly lower than those recommended by national and international expert advisory bodies. For example, the USEPA suggests that radiation exposures above 3×10^{-4} risk (about 0.12 mSv/yr based on the LNT) is not protective of human health or the environment.[165]

Soil radiological cleanup criteria required by USEPA's preliminary remediation goals (PRGs), for example, as related to legacy uranium mining sites, are frequently within the statistical uncertainty of background and, in fact in some cases, less than natural background values. This often results in extensive remedial action costs with no demonstrable health benefits. In fact, cleanup standards as low as USEPA's PRGs often cannot be satisfied with current analytical capabilities. This is an example of where the toxic chemical approach is not appropriate for naturally occurring radionuclides, since the background contains naturally occurring radioactive material, in some cases at levels that exceed the PRG values. Additionally, there are large variations in natural background depending on altitude and geographic location.[166] This is in stark contrast to the background of most chemicals of concern.[156] As mentioned earlier, even BEIR VII acknowledges that epidemiological data below 100 mSv (0.1 Sv) are not sufficient by themselves for risk estimation, yet the USEPA maintains policies that require cleanup to levels where no net benefit to human health or the environment can be detected.

The USEPA SAB recognized in 1992[156] that the USEPA Superfund policy documents, like the risk assessment guidance for Superfund,[167] were being developed to be more consistent with the chemical risk paradigm. In contrast, it also noted that the USEPA radon policy was applying a rule of practicality based on the difficulty of reducing radon levels below 150 Bq/m (4 picocuries/L) within a reasonable budget. The associated risk for its radon policy translates to a lifetime risk of over 1 in 100 for an average person[168] based on the LNT model. More recently, USEPA's approach to radon regulation has been challenged.[169]

Should the Current USEPA Regulatory Radiation Policies Be Reconsidered and Harmonized With the Radiation Protection Philosophy Given the Lessons Learned From Fukushima?

The NCRP issued reports providing guidance on responding to a radiological or nuclear terrorism incident[170,171] and decision-making for late-phase recovery from nuclear and radiological incidents.[172] These recommendations from the NCRP endorse the strategy laid out by the ICRP[173] and apply them to the situation in the United States. This new strategy presents a:

> marked contrast to the current clean-up approach carried out under statutory regulatory provisions that focuses on radiological risk, precautionary decision making, and clean-up goals close to background.[170]

The ICRP suggests that the reference level should be selected in the lower part of the 1 to 20 mSv/yr range (100-2000 mrem/yr[173]). This is much more realistic and achievable than the LNT 10^{-6} risk-based PRGs developed by USEPA, which are approximately 2 to 3 orders of magnitude lower than other guidance provided by NCRP and ICRP.

Although the simplicity of the LNT model used for risk assessment has traditionally been thought to be reasonably conservative, its application has led many to believe that any amount of radiation brings unwarranted risk. This contributes to society's response to make personal decisions to avoid any radiation exposures at all costs, thus potentially resulting in

more societal harm than good. It also drives down cleanup levels, resulting in extraordinary cleanup costs. Furthermore, USEPA has provided guidance stating "approaches that do not follow the remedial program's policies and guidance should not be used at CERCLA remedial sites."[158] It specifically targets any guidance developed by other federal, state, or tribal agencies or by international or national organizations (eg, ICRP, NCRP, and other scientific or professional organizations) and leaves only USEPA guidance available for consultation.

A recent example of where LNT-based guidance may have caused more harm than good is the evacuation in Fukushima, Japan.[174] The Fukushima accident involved no deaths directly related to radiation exposure[175]; however, the evacuation itself caused increased mortality primarily among the elderly individuals.[176-178] Well over a thousand people died from causes related to the evacuation,[179] and the continued exclusion of residents from their homes for extended periods of time. This occurred in spite of the fact that "no significant contamination was found in the patients evacuated from the 20 km zone despite the fact that 48 h had passed between the first explosion and their evacuation."[180] During the Fukushima incident, the public exhibited distrust of radiation experts and confusion regarding what risks radiation from the accident actually presented.[181] The population that evacuated from the area around the Fukushima plant is now at increased risk for mental health problems and other social and psychological problems because of their continued exclusion from their homes, and they are subject to social stigma.[181,182]

The application of the LNT to estimate cancer risks associated with residual contamination, without appropriately considering the uncertainties involved (ie, LNT predictions represent an upper bound estimate of risks, and real risks might in fact be 0), has contributed to continued exclusion of the evacuated Fukushima population from their homes. The same situation occurred at Chernobyl.[183] In addition, recent research has indicated that even when hypothetical radiation risks from residual radioactive contamination are calculated via the LNT model, mass evacuations and relocations like those following Chernobyl and Fukushima have been unjustifiably extensive[184,185] and are almost never part of the optimal response strategy.[174,186,187] Therefore, it is reasonable to question the perceived protectiveness of the LNT model for setting protective standards in LDDR radiation environments.[72] The long-term response to the Fukushima accident will undoubtedly involve, and in fact emphasize, providing accurate information about radiation risks to returning residents and dealing with their fears.[188,189] These fears are exacerbated by strident statements that "there is no safe dose" and "doses outside the USEPA risk range are not protective" and by inaccurate and incomplete information about the uncertainties involved in estimating risks from very low residual radiation doses.[190]

While some of the remedial strategies in response to the Fukushima accident have been retrospectively analyzed and determined to be justified based on an LNT calculation of risk from residual contamination,[191] others response measures have been found to be unjustified.[192] Unrealistic cleanup standards, which fail to properly account for the real possibility that risks from such low doses, may very well be zero, exacerbate public fears, fail to optimize response strategies by ignoring the economic and public health consequences of these actions,[193] and can distort the allocation of resources in the recovery effort. The mission of the USEPA is to protect human health and the environment. The mission of the US Public Health Service is to protect, promote, and advance the health and safety of our nation. Both the USEPA and the USPHS develop policies to accomplish these missions. Although it is acknowledged that the determination of acceptable risk values is a matter of judgment and risk management policy,[194] the USEPA Scientific Integrity Policy explicitly states that science forms the backbone of its decision-making.[195] The science behind low-dose risk estimation and determining cleanup levels is showing that the LNT has the real potential to cause more economic, environmental, and public health harm than good to society.

A comprehensive review of the application of ICRP guidelines and the problems encountered at Fukushima has been documented[196] and offers many lessons. Among the highlights are the following:

> It has been noted that the uncertainties surrounding the crisis itself, in addition to the absence of demonstrated risk at the tiny exposures to the population and the uncertain validity of the linear extrapolation of risk down to such tiny doses, raise serious questions about whether these calculations could provide even an order-of-magnitude guess as to possible health consequences. Further, given the wide range of uncertainties in the risk models used, it is likely that zero effects should be included as a lower bound to the estimates, or even as a central estimate of the likely future effects.
>
> These hypothetical computations of effects are based on assumptions that cannot be validated because the estimated doses are substantially below the level where epidemiology has the ability to detect increases above the natural occurrence. The large number of deaths reported following these theoretical predictions, especially when not contrasted with the normal high occurrence of death, is alarmist and unfounded and has caused severe anxiety and emotional distress in the Japanese population.
>
> It should be recognized, however, that '*balancing' good and harm is not confined to issues associated with radiation exposure. Other non-radiation-related benefits and detriments arising from the protective action must also be considered,* thus going far beyond the scope of radiological protection. (emphasis added)

Fukushima and Chernobyl offer very rare opportunities to learn from the application of radiation protection guidance and strategies in challenging, real-world situations. A frank assessment of the successes and shortcomings of these strategies and how they may impact the agency's cleanup policies is necessary.

The USEPA has taken the position that any residual contamination concentration exceeding the upper risk range of 3×10^{-4} (a dose of about 0.12 mS/yr [12 mrem/yr]) is "not

protective."[165] Is this a valid interpretation, given the very different advice given by the ICRP? Gonzalez[196] state:

> Thus, the public has doubts about what type of exposure the inhabitants of the rehabilitated area will be subject to when the rehabilitation starts. If these people are regarded as members of the public and if the exposure situation is regarded as a planned one, the dose limit of 1 mSv $year^{-1}$ and the corresponding dose constraint could in principle be considered as applicable, therefore *requiring annual doses to the residents to be kept below a few tenths of a millisievert, a restriction that might be considered unrealistic and furthermore rather strange and unreasonable.*[196] (emphasis added)
>
> There was a particular misunderstanding about the appropriate use and application of the dose value of 1 mSv $year^{-1}$. The public tended to regard a dose above this value as dangerous, which created challenges in coping with the aftermath of the accident. The fact that there is little convincing evidence for human health effects below 100 mSv $year^{-1}$ (or 100 times the dose limit) appeared to hold little sway over the level of concern.

The USEPA's interpretation is clearly at odds with the views of the ICRP, which stated,

> The Commission's recommended limits are set at a level which is thought to be associated with a low degree of risk; thus, *unless a limit were to be exceeded by a considerable amount, the risk would still be sufficiently low as not to warrant such countermeasures as would themselves involve significant risks or undue cost*. It is therefore clear that it is not obligatory to take remedial action if a dose-equivalent limit has been or might be exceeded.[197] (emphasis added)

In answer to the question, "Is any Amount of Radiation Safe?," USEPA has explained,

> In setting limits, USEPA makes the conservative (cautious) assumption that any increase in radiation exposure is accompanied by an increased risk of stochastic effects.[58]

Similarly, USEPA has explained,

> LNT also has the great advantage of simplicity, risks from multiple exposures being proportional to the total dose. Given these features of protectiveness and convenience, there is very wide support for LNT in the context of radiation protection, even among scientists and regulators who harbor serious doubts about its scientific validity.[5]

Note that these explanations are based on the assumption that LNT is "conservative" and "cautious." In light of the Fukushima experience, these assumptions are no longer tenable. Others have argued that radiation protection guidelines are confusing and overly stringent, based on the application of LNT at doses far below where risks can actually be observed, and that this had directly observable negative public health consequences.[9,72]

Discussion

In the event of a large-scale domestic radiological dispersal device (RDD) attack, nuclear power plant (NPP) release, or an improvised nuclear detonation (IND), the long-term cleanup challenges will likely have a larger impact on the surrounding communities, cities, and regions, where factors other than potential radiation exposure may become the driving force behind the final cleanup levels. For example, psychosocial, economic, and speed-of-recovery issues all affect the long-term viability and survivability of the affected area. Risks associated with moving an entire population on a temporary or permanent basis may be higher than allowing some low-level exposures from residual contamination. Nondestructive cleanup technologies may prove to be too costly or applicable to only small portions of the recovery effort. Overall costs could become so expensive as to reduce the ability to protect human health and the environment if there are limited resources. Given the potential scope and urgency of the situation following an RDD/NPP/IND scenario, the preference to work toward an acceptable cleanup level (radiation risk paradigm) rather than having to raise a preliminary cleanup goal (chemical risk paradigm) has many political, economic, and societal benefits.

Both radiological and chemical risk paradigms warrant equal consideration when making cleanup decisions. The radiation risk paradigm was included in the Department of Homeland Security guidance with USEPA and other federal agencies' concurrence. The chemical risk paradigm is routinely used at USEPA superfund sites. Both employ risk-based methods and can lead to similar cleanup levels. However, risk is a metric that cannot be measured; only radiation exposure or radioactive surface contamination can be directly measured. Using the USEPA PRG calculators to meet the CERCLA, risk range suggests that the agency knows the risk with a much greater certainty than is scientifically possible. These are based on the LNT model and are inconsistent with the guidance from UNSCEAR, HPS, World Health Organization, and many others. They are tools that foment fear and uncertainty in the affected communities. Instead, a dose-based cleanup approach is more scientific and practical.

There is precedent for the USEPA to quickly change policy based on SAB recommendations. In 1992, the USEPA SAB changed its earlier 1988 recommendation from averaging the radon risk estimates from BEIR IV and ICRP 50 to just using those published in BEIR IV.[198] Recent findings from the ongoing Life Span Study and other peer-reviewed articles as late as 1990 were used to justify this change. This change to the USEPA's radon risk assessment policies is consistent with the goal and objectives of the existing USEPA Scientific Integrity Policy, which requires science to be the backbone of agency decision making.[195] Perhaps, findings or recommendations from a new USEPA SAB review will serve to justify changes

to the agency's existing policies on the use of the LNT model in LDDR radiation environments.

Conclusions

The USEPA is the lead federal agency responsible for protecting human health and the environment from hazardous agents. It carries out this mandate by applying scientific information to promulgate regulations and policies that other federal agencies (eg, NRC and DOE) and states incorporate into their regulations or policies where appropriate or applicable. Thus, the USEPA has a tremendous responsibility to ensure its radiation regulations, policies, and guidance are scientifically sound while providing adequate protection without placing an unnecessary burden on the affected population or organizations subject to them. An objective and unbiased reliance on scientific information to inform decision-making is an integral part of the agency's scientific integrity policy. It sets the foundation for objective discussions among all the affected stakeholders (eg, public, industry, professional organizations, international communities) for determining (1) what are acceptable radiation regulations and policies associated with determining cleanup levels following a large-scale radiological or nuclear incident and (2) what risk assessment model should be used to best represent the risks from LDDR radiation environments when a residual low-level contaminated environment becomes reality.

The scientific understanding of the effects of radiation exposures has evolved since its discovery in the late 19th century. The scientific information supporting the use of the LNT model for LDDR radiation environments developed over that past 70 years but is mainly extrapolated from HDDR environments. The application of the LNT model to determine health risks has created a culture where a few clicks on a radiation dose rate meter equate to cancer in the minds of the public. Society has become so fearful of radiation that unnecessary steps are taken, and other risks are accepted, to avoid even trivial radiation exposures at all costs. This includes potentially life-saving medical examinations, which is recognized as a problem by the many scientific and professional organizations specializing in radiation.

Since the Three Mile Island Nuclear Power Plant accident in 1979, the world has experienced several large-scale nuclear or radiological accidents (eg, Chernobyl, 1986; Goiania, 1987; Fukushima, 2011), affecting millions of people and contaminating millions of hectares of land. The 2011 Fukushima NPP accident is the most recent radiological accident. The accident itself caused no radiation-related deaths[175]; however, the evacuation in response to the accident, combined with the extended exclusion of area residents from their homes, has increased mortality from various stress-related causes. The elderly individuals are especially vulnerable to these effects,[176-178] and over 1600 people died as a result[179] of the response to the Fukushima accident. A retrospective evaluation has concluded that the risk from the evacuation outweighed any hypothetical risk of radiation exposure calculated using the LNT model,[184,185] particularly among the elderly individuals,[199] the evacuation did not protect human health, and was therefore unethical.[200]

Scientists and society continue to learn from these events by questioning how we can strengthen our resilience, reduce the time it takes to resume normal lifestyles, maintain economic viability, and minimize adverse psychological effects. The scientific literature is showing, and scientific organizations acknowledge, that adverse health effects from LDDR radiation exposures are not detectable and that there may be a threshold or even a beneficial effect. These findings contradict the use of LNT model-based predictions.

It is time for the USEPA to reconsider the use of the LNT model in LDDR radiation environments in the regulatory process, especially in the tools it has developed to determine cleanup levels. Change does not occur quickly or easily within government frameworks. It took decades of institutional inertia to arrive at the current regulatory framework. The USEPA SAB recommended "change in the agency culture, change in how the agency works, and increased support for scientists and managers in programs and regional offices responsible for science integration"[201] to occur and thereby improve its regulations and policies. Despite these recommendations by the EPA SAB, there's been no change in the agency's posture or policy associated with using the LNT model for risk assessment and determining cleanup levels in LDDR environments, nor a desire to have it reevaluated by the SAB for more than 20 years.

Objectively evaluating and incorporating the latest scientific evidence on LDDR dose–response relationships for application to the regulatory and policy-making process for risk assessment purposes will (1) ensure science remains the foundation for its decision making, (2) reduce the unnecessary burden of costly cleanups, (3) provide a much needed platform to educate the public on the risks or benefits from LDDR radiation exposures, and (4) harmonize the agency's policies with those recognized by the rest of the radiation scientific community. A continued resistance to conducting a comprehensive review of the latest science regarding LNT-based policies will only diminish the agency's credibility and influence to protect human health and the environment.

Authors' Note

The views expressed in this article are those of the author(s) and do not necessarily reflect the views or policies of the US Public Health Service.

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September 20, 2018

Information Quality Guidelines Staff
Mail Code 2811R
United States Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Request for Correction under the Information Quality Act: 2014 National Air Toxics Assessment (NATA)

Dear Sir or Madam:

The Ethylene Oxide Panel of the American Chemistry Council (ACC), hereby submits this Request for Correction under the Information Quality Act (IQA) of 2000, Section 515 of the 2001 Treasury and General Government Appropriations Act, Pub. L. No. 106-554, the Office of Management and Budget (OMB) Guidelines for Ensuring and Maximizing the Quality, Utility, and Integrity of Information Disseminated by Federal Agencies,[1] and the Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (EPA).[2] ACC represents producers and users of ethylene oxide (EO).

ACC seeks the correction of EO information disseminated in the 2014 update to the National Air Toxics Assessment (NATA), released on August 22, 2018.[3] The 2014 NATA relies upon the "Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)"[4] to determine the risk value for EO. As detailed below, the 2014 NATA does not meet the IQA's data quality requirements because the EO IRIS Assessment is not the best available science. Therefore, the 2014 NATA risk estimates for EO should be withdrawn and corrected to reflect scientifically-supportable risk values. Moreover, EPA should not use the EO IRIS Assessment's inhalation unit risk estimate (URE) of 5×10^{-3} per $\mu g/m^3$, which corresponds to a one-in-a-million increased cancer risk concentration of 0.1 parts per trillion (ppt), to calculate EO risk in

[1] 67 Fed. Reg. 8452 (Feb. 22, 2002) (OMB Guidelines).

[2] Available at https://www.epa.gov/sites/production/files/2017-03/documents/epa-info-quality-guidelines.pdf (EPA Guidelines).

[3] Available at https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results (2014 NATA).

[4] EPA/635/R-16/350Fa (December 2016) (EO IRIS Assessment).

its ongoing Clean Air Act (CAA) Section 112 risk and technology review (RTR) rulemakings and other regulatory actions.[5]

As producers and users of EO, ACC members are directly impacted by the errors in the 2014 NATA. The risk estimates based on the EO IRIS value have significant regulatory implications for ACC member companies who produce commercial products of value to consumers using EO. Correcting these deficiencies will result in more accurate estimates of potential risk that will lead to improved regulatory outcomes, the dissemination of more accurate information to the public, and overall reduced misconception.

This Request for Correction is organized into four sections. The Executive Summary provides a high level overview of the key reasons why the 2014 NATA does not meet the objectivity, accuracy, integrity and utility requirements of the IQA and the OMB and EPA Guidelines due to its reliance on the EO IRIS Assessment. The second section provides background information on the 2014 NATA and the EO IRIS Assessment. The third section highlights the information in the EO IRIS Assessment that is not scientifically supportable. In the last section, each of the key deficiencies in the EO IRIS Assessment is discussed in detail with supporting scientific evidence.

I. Executive Summary

In the 2014 NATA, EPA relies on updated benchmarks for several substances, including EO. For EO, EPA updated its cancer risk calculations to reflect the URE in the EO IRIS Assessment. The use of the URE value, however, results in inaccurate and misleading conclusions about EO risk.

The EO IRIS Assessment is based on a supralinear spline slope for lymphoid and breast cancer exposure-response analyses from an epidemiology study conducted by the National Institute for Occupational Safety and Health (NIOSH). **This supralinear risk assessment model predicts high risk at low exposures, lower risk at higher exposures, and estimates an unrealistically low concentration of 0.1 ppt.** This 10^{-6} risk specific concentration (RSC) is the lower bound lifetime chronic exposure level of EO that corresponds to an increased cancer risk of one-in-a-million. **Both the supralinear slope and the RSC are implausible based on the epidemiological evidence and biological mode of action.**

[5] In a recently proposed RTR rule, EPA solicits comment on whether it should ban the use of EO for one of the source categories. *NESHAP; Surface Coating of Large Appliances; Printing, Coating, and Dying of Fabrics and Other Textiles; and Surface Coating of Metal Furniture Residual Risk and Technology Reviews,* 83 Fed. Reg. 46262, 46294 (Sept. 12, 2018).

In addition, these implausible levels lack utility for regulatory purposes. **The RSC in the EO IRIS Assessment is 19,000 times lower than the air-concentration equivalent yielding normal, endogenous levels of EO in the human body. Likewise, the RSC is orders of magnitude lower than ambient levels of EO.** Thus, if the EO IRIS Assessment is to be believed, normal human metabolism and/or breathing ambient air is sufficient to cause cancer. The EO IRIS Assessment does not provide a meaningful basis for assessing and managing risk for EO.

As outlined below, the EO IRIS Assessment is substantially flawed and can be corrected by using the approach published by Valdez-Flores et al. (2010),[6] which models potential mortality excesses for lymphohematopoietic tissue (LH) cancers from the two strongest epidemiological studies (NIOSH and Union Carbide Corporation (UCC)) using a log-linear Cox proportional hazard model. **Valdez-Flores et al. (2010) estimated ranges for the maximum likelihood estimate (MLE) and the 95% lower confidence limit of the environmental concentration corresponding to an extra risk of one in a million [LEC (1/million)] of, respectively, 1.5-9.2 parts per billion (ppb) and 0.5-1.2 ppb.** The major reason for the large difference between these values and the EO IRIS Assessment estimates is that the IRIS Program uses a supralinear spline model and Valdez-Flores et al. (2010) uses the log-linear Cox model.

EPA's cancer risk assessment guidelines caution that "a steep slope [i.e., supralinear] also indicates that errors in an exposure assessment can lead to large errors in estimating risk."[7] This is relevant to the EO IRIS Assessment because the NIOSH exposure model has a much higher level of uncertainty between the late 1930s and 1978 when there was inadequate (1976-78) or no exposure data (<1976) to independently validate the model. Furthermore, the NIOSH exposure model was modified when estimating exposures prior to 1978 by fixing the effect of a key variable (calendar year) in the model.

Specifically, Hornung et al. (1994) determined that Calendar Year is a major predictor of exposure in the model after 1978, but they did not allow this variable to impact exposures in the model prior to 1978.[8] Hornung et al. (1994) surmised that Calendar Year acts as a surrogate for improvement in work practices. **Thus, the arbitrary decision to alter the model prior to 1978 essentially assumes there were no evolving work practices in contract sterilizer facilities**

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[6] Valdez-Flores C, Sielken RL Jr, Teta MJ. 2010. Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regul Toxicol Pharmacol, 56(3): 312-20.

[7] EPA, Guidelines for Carcinogen Risk Assessment (March 2005), at 3-19. Available at https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

[8] Hornung RW, Greife AL, Stayner LT, Steenland NK, Herrick RF, Elliott LJ, Ringenburg VL, Morawetz J. 1994. Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. Am J Ind Med, 25(6): 825-36.

between 1938 and 1977 that influence exposure to workers. The EO IRIS Assessment did not critically evaluate the assumptions and uncertainties of the NIOSH exposure model.

Moreover, the EO IRIS Assessment makes an unsubstantiated and counter-intuitive claim that the EO sterilization process was historically constant and stable prior to 1978. Yet, even the authors of the NIOSH study predict higher exposures before installation of engineering controls ("e.g., increased ventilation and better door seals") in 1978, when OSHA standards were higher.[9] **Below, we provide information on evolving regulatory standards, residue levels of EO, equipment, engineering and processing practices that indicate that the NIOSH exposure model incorrectly predicted that exposures would decrease in earlier years compared to the 1970s for the most exposed jobs (e.g. sterilizer operator). In general, *underestimating exposures will overestimate risk*, and the EPA cancer risk assessment guidelines caution that use of a supralinear model will further exacerbate the impact of these exposure errors.**

The rationale for selecting the supralinear spline model is based on incorrect statistical procedures and visual misrepresentation of the data. The EO IRIS Assessment incorrectly calculates the statistical significance (e.g., p- and AIC values) of the supralinear spline dose-response model because it fails to account for the statistical impact of the trial-and-error exploration of different arbitrary values used in the EO IRIS Assessment's dose-response model, such as the exposure level where the slope changes in the model from a very steep slope to a shallow slope (i.e. the "knot").[10] In addition, the figures used to compare visual fits use categorical data rather than the individual cases that were modeled. Once the individual cases are used, the log-linear Cox model fits the data just as well as the more complex and ill-advised supralinear spline model. The log-linear Cox model best meets the objective of selecting the more parsimonious model with fewer assumptions and variables.

Biologically, selection of the log-linear Cox model is more consistent with the mode of action for EO. This is supported by the EO IRIS Assessment, which concludes it is "highly plausible that the dose-response relationship over the endogenous range is sublinear … that is, that the slope of the dose-response relationship for risk per adduct would increase as the level of endogenous adducts increases."[11]

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[9] Steenland K, Stayner L, Greife A, Halperin W, Hayes R, Hornung R, Nowlin S. 1991. Mortality among workers exposed to ethylene oxide. N Engl J Med, 324(20): 1402-07.

[10] *See, e.g.,* Li W, He C, Freudenberg J. 2011. A mathematical framework for examining whether a minimum number of chiasmata is required per metacentric chromosome or chromosome arm in human. Genomics, 97(3): 186-92.

[11] EO IRIS Assessment, at 4-95.

Both the UCC and NIOSH studies should be included in the dose-response modeling so that the risk estimates are based on the best available human data. Although the NIOSH study cohort is much larger, both studies have comparable power for males when considering the number of events of interest, i.e., lymphohematopoietic tissue cancers. The EO IRIS Assessment excludes the UCC cohort based primarily on a comparison of the exposure assessments for both studies. The EO IRIS Assessment dismisses the UCC exposure estimates as "crude," "largely-uninformative," "much less extensive," and "greater likelihood for exposure misclassification," as compared with the NIOSH study, which is described as "well-validated" and "high-quality." These descriptions lack objectivity and obscure the fact that the majority of the UCC cohort exposure estimates are based on contemporary data from different plants with identical or comparable processes. **Although the NIOSH exposure model was validated with data after 1978, there were no contemporary data between the late 1930s and mid-1970s to validate the final model. Thus, the UCC exposure assessment uncertainties are no greater than the NIOSH study uncertainties and, therefore, are not a valid reason to exclude the UCC cohort.**

The EPA Science Advisory Board's (SAB) peer review of the draft EO IRIS Assessment did not remedy the shortcomings of the final EO IRIS Assessment. The presumption of objectivity that sometimes attaches to documents that have been peer reviewed does not apply in this case because authors of the NIOSH study influenced the analysis of the data as well as the responses to the SAB's comments. This influence compromised the objectivity and independent analysis of the NIOSH study, and especially the NIOSH exposure model, in the draft and final EO IRIS Assessments.

II. The 2014 NATA and the EO IRIS Assessment

The 2014 NATA uses emissions information to help state, local, and tribal air agencies identify which pollutants, emission sources, and places may warrant a better understanding for any possible risks to public health from air toxics. EPA further uses NATA results to improve data in emission inventories; identify where to expand air toxics monitoring; help target risk reduction activities; identify pollutants and source types of greatest concern; help decide what other data to collect; better understand risks from air toxics; and work with communities to design their own assessment.

The 2014 NATA results list EO emissions information across a range of categories, including location, cancer risks, hazard quotients, source type (e.g., stationary sources, mobile, airports, etc.). In building the NATA, EPA must select specific risk levels for certain air toxics that can lead to determinations of acceptable or unacceptable thresholds. Since air toxics have no universal, predefined risk levels that clearly represent acceptable or unacceptable thresholds,

EPA makes case-specific determinations and general presumptions that apply to certain regulatory programs that further inform the interpretation of risk in the NATA. These benchmarks are drawn from a range of sources and updated. EPA notes that several substances' benchmarks were updated since the 2011 NATA, including EO. Specifically, EPA states that its risk value for EO was updated in 2016—the newly finalized IRIS value. As such, EPA updated its cancer risk calculations to reflect this new updated benchmark value. Due to the use of the EO IRIS value, more areas show elevated risks driven by EO in the 2014 NATA than in the 2011 NATA, even if emissions levels have stayed the same, or even decreased, in these areas.

The alleged elevated cancer risk driven by EO in the 2014 NATA has already caused alarm in some communities around facilities with EO emissions. This, in turn, has created media attention, and coverage of the issue has created further confusion and concern in the surrounding community. All of this could have been avoided had EPA relied on the best available science in calculating the unit risk estimate for cancer.

As discussed in detail below, the use of the updated EO IRIS value in the 2014 NATA and its Technical Support Document is extremely problematic given the EO IRIS Assessment's numerous shortcomings. A simple comparison of the results of the EO IRIS Assessment to the "real world," however, demonstrates its lack of credibility. Specifically, the RSC is 19,000 times *lower* than the normal, endogenous levels of EO in the human body. Likewise, the RSC is orders of magnitude *lower* than ambient levels of EO. Thus, if the EO IRIS Assessment is to be believed, normal human metabolism and/or breathing ambient air, without more, is sufficient to cause cancer. It strains scientific credibility to conclude that the EO IRIS Assessment presents a legitimate basis for determining risk for EO.

III. Request for Correction

The 2014 NATA relies upon the EO IRIS Assessment's inhalation URE of 5×10^{-3} per $\mu g/m^3$ to calculate EO risk. This URE implies a corresponding RSC of 0.1 ppt. The use of these values, however, results in inaccurate and misleading conclusions about EO risk because they are not supported by the scientific data. The RSC is also unrealistic, given that it is orders of magnitude lower than levels of EO in ambient air and levels that are consistent with normal, endogenous levels of EO present in human bodies.

A more reasonable and scientifically supportable approach to an exposure response analysis yields ranges for the MLE (1.5-9.2 ppb) and LEC (0.5-1.2 ppb) that are more than three orders of magnitude greater than the RSC.[12] Moreover, the ranges of MLE and LEC values are

[12] Valdez-Flores et al. (2010).

conservative because (a) extra risk was calculated despite no statistically significant slope in the exposure-response analyses; (b) the NIOSH data was included without adjustment for likelihood of underestimation of exposures; and (c) the limited evidence of cancer risk based on the entire body of epidemiologic evidence (see Appendix 2). The 2014 NATA risk estimates for EO should be withdrawn and corrected to reflect these risk values. Moreover, EPA should not use the EO IRIS Assessment's RSC of 0.1 ppt or URE of 5 x 10^{-3} per $\mu g/m^3$ to calculate EO risk in its ongoing CAA Section 112 risk and technology review or other rulemakings.

A. The 2014 NATA Does Not Meet the Objectivity, Integrity, and Utility Requirements of the IQA and the OMB and EPA Guidelines.

Congress enacted the Information Quality Act (IQA) to "ensur[e,] and maximiz[e,] the quality, objectivity, utility and integrity of information (including statistical information) disseminated by Federal agencies" such as EPA.[13] The IQA required OMB to issue government-wide guidance, which each federal agency was to follow in its issuance of its own guidelines. The purpose of the EPA Guidelines is to apply the OMB Guidelines to the Agency's particular circumstances, and to "establish administrative mechanisms allowing affected persons to seek and obtain correction of information … disseminated by the agency that does not comply with the [OMB] guidelines…."[14] The 2014 NATA, therefore, must meet the OMB Guidelines as well as the EPA Guidelines.

OMB Guidelines include clear definitions to guide agency practices in adhering to the IQA. These include:

- "'Information' means any communication or representation of knowledge such as facts or data, in any medium or form, including textual, numerical, graphic, cartographic, narrative, or audiovisual forms."[15]

- "'Influential,' when used in the phrase 'influential scientific, financial, or statistical information,' means that the agency can reasonably determine that dissemination of the information will have a clear and substantial impact on important public policies or important private sector decisions."[16]

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[13] *See* Pub. L. No. 106-554. The IQA was developed as a supplement to the Paperwork Reduction Act, 44 U.S.C. §3501 et seq., which requires OMB, among other things, to "develop and oversee the implementation of policies, principles, standards, and guidelines to …apply to Federal agency dissemination of public information."

[14] Pub. L. No. 106-554.

[15] OMB Guidelines, at 8460.

[16] *Id.*

- "'Objectivity' involves two distinct elements, presentation and substance. 'Objectivity' includes whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner.... In addition 'Objectivity' involves a focus on ensuring accurate, reliable, and unbiased information. In a scientific, financial, or statistical context, the original and supporting data shall be generated, and the analytic results shall be developed, using sound statistical and research methods."[17]

- "'Utility' refers to the usefulness of the information to its intended users, including the public. In assessing the usefulness of information that the agency disseminates to the public, the agency needs to consider the uses of the information not only from the perspective of the agency but also from the perspective of the public. As a result, when transparency of information is relevant for assessing the information's usefulness from the public's perspective, the agency must take care to ensure that transparency has been addressed in its review of the information."[18]

The 2014 NATA is influential scientific risk assessment information and must adhere to a rigorous standard of quality.[19] The 2014 NATA is "influential" scientific risk assessment information as set forth in the EPA Guidelines because it "will have or does have a clear and substantial impact (i.e., potential change or effect) on important public policies or private sector decisions" and involves "controversial scientific ... issues."[20] Results from the NATA are used by government agencies, non-governmental organizations, and air quality experts to gauge which hazardous air pollutants (HAP) and emission sources may raise health risks in certain places. These places are then given more attention and EPA uses the NATA to, among other things, target ways to achieve risk reduction.

The NATA can also lead to the development of local community-supported plans to reduce emissions as presented in each NATA version's results. Additionally, the National Research Council (NRC) has recognized the NATA as one of the largest EPA efforts to "develop baseline cancer risk estimates and hazard index calculations using dose-response information and exposure estimates."[21] In this context, NRC further acknowledges the importance of the NATA as a "tool for exploring control priorities" and its function "as a preliminary attempt to establish a

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[17] *Id.* at 8459.

[18] *Id.*

[19] Quality includes objectivity, utility, and integrity.

[20] *See* EPA Guidelines, at 19-20 (internal citations omitted); OMB Guidelines, at 8455.

[21] National Research Council, "Air Quality Management In the United States" (2004), at 247. Available at https://www.nap.edu/read/10728/chapter/1.

baseline for tracking progress in reducing HAP emissions."[22] Therefore, the 2014 NATA, and its underlying data, must adhere to a rigorous standard of quality, including meeting the higher standard of reproducibility.

With regard to the analysis of risks to human health, safety and the environment maintained or disseminated by the agencies, the OMB and EPA Guidelines also require either adoption or adaption to "the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996 (42 U.S.C. 300g-1(b)(3)(A) & (B))."[23] In ensuring the objectivity of influential scientific risk information (i.e., the substance of the information is accurate, reliable and unbiased), the EPA Guidelines have adapted these principles by requiring the use of the "best available science and supporting studies" and the collection of data using by "accepted methods or the best available methods" using "a 'weight-of-evidence' approach that considers all relevant information and its quality."[24]

EPA has failed to apply a transparent and systematic weight-of-evidence approach in assessing the cancer risks of EO exposures in the 2014 NATA. Moreover, as detailed below, because the 2014 NATA relies upon the EO IRIS Assessment to determine the risk value for EO, the 2014 NATA is not based on the best available science.

B. The EO IRIS Assessment Does Not Meet Scientific Standards from Multiple Standpoints.

The EO IRIS Assessment is not the best available science because it: (1) exclusively relies on a NIOSH study despite its flawed exposure assessment; and (2) applies a supra-linear spline model, which is implausible based on the epidemiological and biological evidence and deficient due to statistical miscalculations and visual misrepresentations.

1. The EO IRIS Assessment incorrectly describes the NIOSH exposure model as a "state-of-the-art" validated regression model to estimate historical exposures prior to 1978. In fact, this "state-of-the-art" validated model was tested with post-1978 data only and arbitrarily altered for years prior to 1978. Specifically, a variable considered to be a major predictor of exposure after 1978 was not allowed in the model to impact exposures prior to 1978. The

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[22] *Id.*

[23] *See* EPA Guidelines, at 22-23; OMB Guidelines, at 8460.

[24] *See* EPA Guidelines, at 21-22. "In this approach, a well-developed, peer-reviewed study would generally be accorded greater weight than information from a less well-developed study that had not been peer-reviewed, but both studies would be considered." *Id.* at 26. The definition of best available science mirrors that articulated in Chlorine Chemistry Council v. EPA, 206 F.3d 1286 (D.C. Cir. 2000), referring to "the availability at the time an assessment is made." *See* EPA Guidelines, at 23.

reliability, validation and likelihood of exposure misclassification prior to 1978 were not objectively evaluated.

2. The results of NIOSH's statistical model for exposures prior to 1978 were not provided in the 2014 Draft EO IRIS Assessment or in the cited NIOSH publications. In the appendices of the final EO IRIS Assessment, two new figures (Figures D-22 and D-33) present new information on estimated exposures by worker, but no explanation or critical evaluation was added. There is a lack of transparency in the EO IRIS Assessment of these influential data used to derive the EO cancer slope factor.

3. The EO IRIS Assessment repeatedly asserts that the NIOSH exposure estimates were well-validated using a state-of-the-art model, when in fact there was no validation of exposure estimates prior to 1978. These assertions regarding verification procedures are incorrect for the late 1930s to 1978.

4. In response to public and SAB comments questioning the lower than expected exposures in earlier years predicted by the statistical regression model, the IRIS Program states that the decrease is related to the sterilizer volume. In other words, the model predicts that smaller sterilizer volume results in lower exposures. This response essentially uses the output of the model to answer a question about whether the model assumptions are correct, instead of independently verifying the validity of these assumptions. This circular reasoning does not address the underlying concern of whether the model assumption that Sterilizer Volume has an inverted parabolic (that is, an upside-down U-shaped) relationship with predicted EO exposure is correct. It also does not address whether other factors that might result in increased exposure during early years were properly accounted for in the model.

5. The EO IRIS Assessment makes the unsubstantiated claim that "the sterilization processes used by the NIOSH cohort workers were fairly constant historically, unlike chemical production processes, which likely involved much higher and more variable exposure levels in the past."[25] In fact, there was an evolution in technology and practices associated with the sterilization processes between the late 1930s and early 1970s. Data and information from industrial sterilization operators and the literature refute this claim.

6. Comparisons of relative reliability made between the NIOSH and UCC studies are inaccurate. These comparisons were a key basis upon which the IRIS Program rejected the UCC Study as a source of epidemiology study data for cancer risk assessment. The EO IRIS Assessment does not acknowledge and appropriately consider limitations of the NIOSH

[25] EO IRIS Assessment, at 4-4.

exposure assessment posed by low extrapolations of NIOSH cohort exposures to EO prior to the late 1970s without any corroborating data or any supporting engineering/process considerations derived from or directly relevant to that period of time.

7. The EO IRIS Assessment relies solely on the NIOSH study of sterilant workers and fails to incorporate the important findings from the UCC study of workers in EO producing and using operations. The IRIS Program considered and characterized three factors in its selection of the NIOSH study: cohort size, exposure data, and confounding. Based on these factors, the IRIS Program dismissed the UCC study as a basis for EO cancer risk estimation. In considering cohort size, the IRIS Program ignored the most important comparison—the number of lymphohematopoietic tissue cancers, not the total cohort size.

8. The use of the supralinear spline model for the lymphoid and breast cancers in the final EO IRIS Assessment is based on an invalid statistical analysis. Because the analysis did not correctly calculate degrees of freedom associated with that fitted model, it contains erroneous measures of absolute and relative goodness of fit of that model. When both the p-values and Akaike Information Criterion (AIC) values characterizing fit quality are corrected, the supralinear spline model does not fit the NIOSH lymphoid tumor data statistically significantly better than the log-linear Cox model.

9. The selection of the supralinear spline model for the lymphoid tumors is also based on misleading illustrations of "visual fits" that do not convey either the actual data that were fit or the relative goodness of fit to these data of log-linear and supralinear spline models. Only in a footnote does the IRIS Program indicate that the visual comparison misrepresents the log-linear model being compared. Consequently, and erroneously, the fit to the data appears far worse than the supralinear spline model. The data plotted in that figure also were summary data that misrepresent the true magnitude of the scatter of the data that were used for model fitting.

10. The selection of a spline model as the preferred model for EO cancer risk estimation assumes a supralinear increase in tumor response in the low-dose exposure region with a subsequent plateauing of response at higher exposures. The body of cancer epidemiologic studies, including the NIOSH studies, does not support such a pattern of risk. While certain NIOSH sub-analyses suggest increases in male lymphoid tumors and female breast cancers, the findings are limited to the highest cumulative exposure groups, not the lowest.

11. The use of a supralinear spline model for cancer risk estimation is inconsistent with the assumed mode-of-action of EO toxicity and tumorigenicity. Such a model predicts higher risk at low exposures compared to risks predicted at higher exposures, which is contradicted by the well-understood mode of action of EO in experimental animals and humans

as described in the EO IRIS Assessment. Thus, the EO IRIS Assessment relies on human cancer risk estimates based on spline-model dose-response extrapolations that are internally inconsistent with its own evaluation of the mode of action of EO. The mean air concentration equivalent to the endogenous concentration in non-smoking humans with no known EO exposures is 1.9 ppb (range 0.13-6.9 ppb; continuous), which is 19,000 times greater than the EO IRIS RSC of 0.1 ppt.[26] An alternative LEC (1/million) of 0.5-1.2 ppb is a more pragmatic, science-based approach for EO risk assessment.

12. The statistical, epidemiological and biological evidence does not support the selection of supralinear spline models to fit the NIOSH study data in the EO IRIS Assessment. A more scientifically sound conservative alternative is to use the Valdez-Flores et al. (2010) approach, which incorporates all the available data from the two strongest human studies (NIOSH and UCC). This approach has been adopted by the European Commission's Scientific Committee on Occupational Exposure Limits.[27]

IV. Because the 2014 NATA Relies Upon the EO IRIS Assessment to Determine the Risk Value for EO, the 2014 NATA Is Not Based on the Best Available Science.

1. The EO IRIS Assessment incorrectly describes the NIOSH exposure model as a "state-of-the-art" validated regression model to estimate historical exposures prior to 1978. In fact, this "state-of-the-art" validated model was tested with post-1978 data only and arbitrarily altered for years prior to 1978. Specifically, a variable considered to be a major predictor of exposure after 1978 was not allowed in the model to impact exposures prior to 1978. The reliability, validation and likelihood of exposure misclassification prior to 1978 were not objectively evaluated.

The EO IRIS Assessment's evaluation of the cancer potency of EO is dependent on an analysis of commercial sterilization worker exposure conducted by NIOSH. The NIOSH EO data for the sterilization work cohort were nearly all collected between 1978 and 1986 at 20 different facilities, but included just seven mean values based on 23 exposure measurements for the period 1976-77.[28] Ultimately, of the 20 facilities, 16 facilities were eliminated from the

[26] Kirman CR, Hays SM. 2017. Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. Regul Toxicol Pharmacol, 91: 165-72.

[27] *See* Recommendation from the Scientific Committee on Occupational Exposure Limits for ethylene oxide, SCOEL/SUM/160 (June 2012).

[28] Hornung et al. (1994).

exposure assessment for lack of personal sampling, documentation of sampling, or links of sampling to job categories.

Based on the available worker data, the workers included in the NIOSH study cohort were employed in the sterilization industry as early as the 1930s. Noting that "there were no measurement data prior to 1976," Hornung et al. (1994) describe the statistical model[29] developed to estimate NIOSH EO-cohort worker exposures based on data collected after 1978. That model was applied to estimate worker exposures over a large timespan (1935-1975) during which not a single observed measurement was available to validate the application of that model extrapolation procedure.

Although the NIOSH statistical regression model estimated exposure measurements after 1977 with reasonable reliability, Hornung et al. (1994) highlighted that post-1978 regulatory standards and consequent progressively stringent operational EO-exposure controls accounted for the pronounced decreasing trend in measured NIOSH-cohort EO exposures that occurred after 1978. Prior to 1978, these EO standards and controls were largely or entirely absent. Thus, they were irrelevant to most of the 1935-1975 timespan, during which time the NIOSH statistical model was applied to estimate historical worker exposures without any empirical physical-modeling basis for direct validation.

The final statistical model selected to predict the natural logarithm (ln) of EO exposure included two nonlinearly modeled variables which were determined to be the two most EO-predictive variables identified: Calendar Year ("Year") and Sterilizer Volume ("Cubic Feet"). These two variables were each modeled to have an inverted parabolic relationship to predicted ln(EO) levels, resulting in predicted peak EO exposures to occur during 1978 as a function of Year. Hornung et al. (1994) note that their final statistical model arbitrarily set the value of Year to be 1978 for all years prior to 1978, explaining that:

> Since we felt that the decrease in ETO levels after 1978 (independent of engineering controls) was explained by improved work practices after ETO was identified as a potential carcinogen, we set each predicted ETO level prior to 1978 equal to the predicted level in 1978. Variation in exposure levels prior to 1978 were modeled as a function of the remaining terms in the model with the calendar year effect fixed at 1978. Therefore, there was no extrapolation by calendar year prior to 1978.

[29] Steenland NK, Stayner LC, Griefe AL. 1987. Assessing the feasibility of retrospective cohort studies. Am J Ind Med, 12: 419-30; Greife AL, Hornung RW, Stayner LG, Steenland KN. 1988. Development of a model for use in estimating exposure to ethylene oxide in a retrospective cohort mortality study. Scand J Work Environ Health, 14(Suppl 1): 29-30.

Thus, the "validated" model was arbitrarily and selectively altered for years prior to 1978 by fixing the calendar year value to 1978. Nonetheless, for the same period prior to 1978, the model still predicts that lower EO sterilizer volumes were associated with lower occupational EO exposures—a prediction made without any independent, pre-1978 measurement-based or physical-modeling-based evidence supporting such an association during that period. The IRIS Program should have questioned the reliability and validation of the model prior to 1978, and objectively considered the likelihood of exposure misclassification during this period.

2. **The results of NIOSH's statistical model for exposures prior to 1978 were not provided in the 2014 Draft EO IRIS Assessment or in the cited NIOSH publications. In the appendices of the final EO IRIS Assessment, two new figures (Figures D-22 and D-33) present new information on estimated exposures by worker, but no explanation or critical evaluation was added. There is a lack of transparency in the EO IRIS Assessment of these influential data used to derive the EO cancer slope factor.**

A basic standard quality expectation for a peer-reviewed publication of a statistical model for exposure is that the results section should include summary of the output of the model; in other words, the estimated exposures resulting from the model. Neither the NIOSH exposure modeling publications nor the NIOSH epidemiology studies that rely on this model provide any descriptive summary of exposures estimated by the model prior to the late 1970s. The IRIS Program should have independently evaluated the exposure data, especially after ACC provided the summary of NIOSH exposures by job (reprinted below as Figure 1).

Figures D22 and D23 in the EO IRIS Assessment are graphs of estimated annual exposures for the entire cohort by worker, but not by job. However, there is no discussion or analysis of these graphs in either Appendix D or the main report. These figures are less informative in understanding how the NIOSH exposure model estimated exposure by job because these figures are based on each worker who could have different job assignments. Nevertheless, the 95th percentile of annual exposures of the NIOSH cases in Figure D-23 has a very similar pattern of exposures as the job with the maximum exposure in Figure 1 below.

As described below, neither Hornung et al. (1994) nor the IRIS Program offer any realistic explanation for the counterintuitive trend backward in time from the late 1970s that is predicted by the NIOSH statistical regression model, other than such a trend just happens to be what that statistical model predicts. Thus, there is a lack of transparency and independent critical evaluation of the exposure estimates of the NIOSH exposure model in the EO IRIS Assessment.

Moreover, the derivation of the NIOSH statistical regression model can no longer be reproduced, because the raw data on which it was based no longer exist.[30]

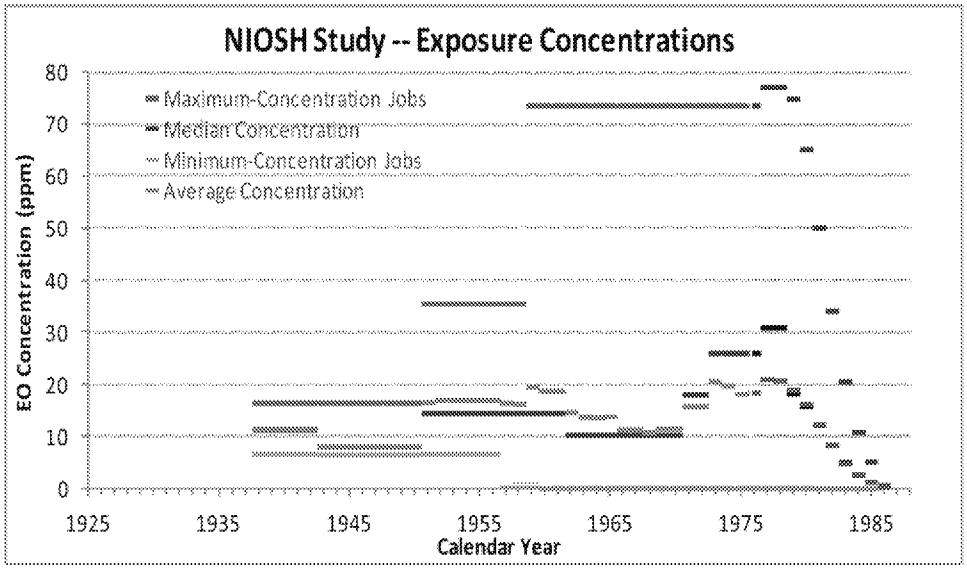

Figure 1. NIOSH statistical regression model predictions of 8-hour time-weighted average exposure to EO by job in each calendar year. This summary data for each job was provided by NIOSH and was used to estimate exposures for participants in the NIOSH cohort based on job code. This figure appeared on page 173 of Appendix M ("Comments on NIOSH Exposure Papers: Greife et al. (1988) and Hornung et al. (1994)") of Comments on the Revised External Review Draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, Docket ID No. EPA-HQ-ORD-2006-0756 submitted to EPA by ACC on October 11, 2013, but did not appear either in Hornung et al. (1994) or any of the draft EO IRIS Assessments reviewed by SAB.

[30] Appendix H (Summary of 2007 External Peer Review and Public Comments And Disposition) of the EO IRIS Assessment states, "[i]n response to the panel's suggestion that the Hornung analysis represents an 'invaluable opportunity' for further analysis of the impact of possible errors in exposure estimation, the EPA investigated the possible use of the 'errors in variables' approach (page 27 of the panel report). Steenland visited the NIOSH offices in Cincinnati in order to review the data and assess whether it would support an errors-in-variables analysis. Unfortunately, the electronic data files used in the [NIOSH] exposure analysis were no longer available, so that analysis based on the errors-in-variables approach was not possible." *Id.* at H-28. Thus, the raw data on which NIOSH relied to derive its statistical regression model used to extrapolate historical NIOSH-cohort exposures to EO prior to the late-1970s, when measures of workplace EO first began to be made, no longer exist—implying that there is no longer any way to validate the claim by Hornung et al. (1994) that their model was able to predict the 85% of the variation in log values of EO concentrations measured starting in the late-1970s. Even if that claim were true, it has no logical bearing on the ability of that model to generate accurate extrapolations of occupational exposure to EO back in time prior to the late 1970s when, as emphasized by Hornung et al. (1994), occupational conditions were quite different because none or virtually none of many sterilization technology changes and sterilization workplace practices, which only began to be adopted starting in the late 1970s to greatly reduce EO exposures (as reflected by NIOSH-cohort exposure measures made starting in the late 1970s to which the NIOSH statistical regression model was fit), were in place prior to that time.

The pattern shown in Figure 1 indicates generally lower exposures for earlier time periods when the crudest technology was used under the least stringent worker protection standards. The SAB considered this pattern to be "surprising," as discussed in greater detail in Section 4, below. Indeed, the pattern of the NIOSH exposure data by job in Figure 1 is the reverse of patterns of historical exposure levels from published studies of exposures to volatile chemicals through time with improvements in technology and increased worker protection requirements[31] as illustrated in two relevant examples (Figures 2 and 3).

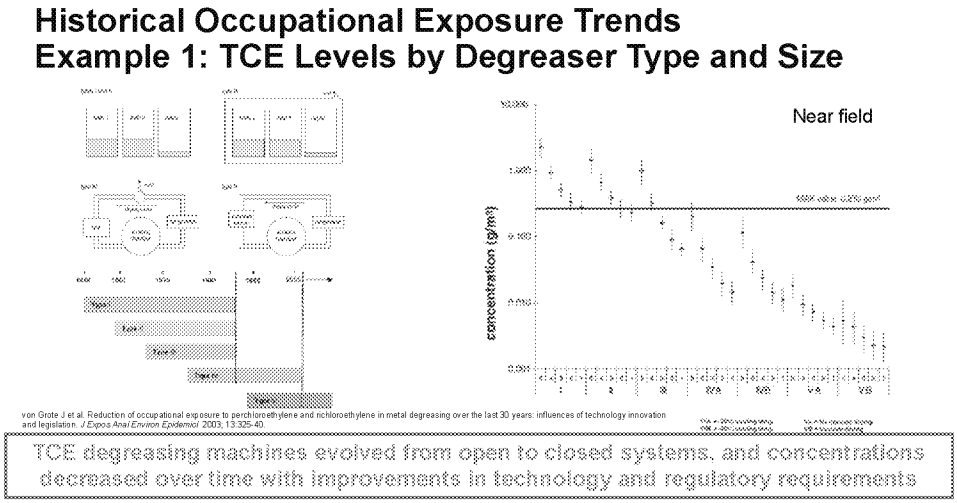

Figure 2. Historical occupational exposure trends, Example 1: TCE levels by degreaser type and size. Source: von Grote et al. (2003b).

[31] *E.g.*, von Grote JHM. 2003a. Occupational Exposure Assessment in Metal Degreasing and Dry Cleaning – Influences of Technology Innovation and Legislation. Doctoral Dissertation, Swiss Federal Institute of Technology, Zürich. Available at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.628.1123&rep=rep1&type=pdf; von Grote J, Hürlimann C, Scheringer M, Hungerbühler K. 2003b. Reduction of occupational exposure to perchloroethylene and trichloroethylene in metal degreasing over the last 30 years: influences of technology innovation and legislation. J Expo Anal Environ Epidemiol, 13: 325-40; von Grote J, Hürlimann C, Scheringer M, Hunger K. 2006. Assessing occupational exposure to perchloroethylene in dry cleaning. J Occup Envir Hyg, 3: 606-19.

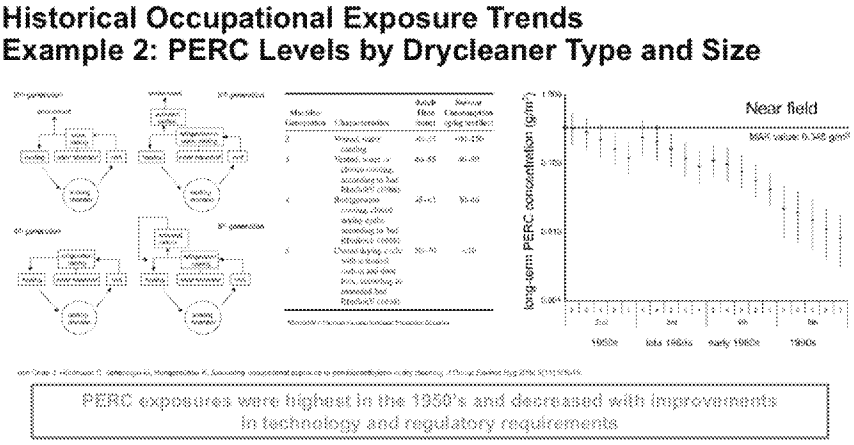

Figure 3. Historical occupational exposure trends, Example 2: PERC levels by dry cleaner type and size. Source: von Grote et al. (2006).

3. The EO IRIS Assessment repeatedly asserts that the NIOSH exposure estimates were well-validated using a state-of-the art model, when in fact there was no validation of exposure estimates prior to 1978. These assertions regarding verification procedures are incorrect for the late 1930s to 1978.

Assertions made in the EO IRIS Assessment about independent evaluation of model estimates are inaccurate. Table 1 lists the statements in the EO IRIS Assessment related to the UCC and NIOSH exposure assessments.

Table 1: List of EO IRIS Assessment statements regarding UCC or NIOSH exposure assessment

Page Number	Description of UCC exposure	Description of NIOSH exposure
1-1		Had a well-defined exposure assessment for individuals
1-2		"high-quality" study based on several attributes, including availability of individual worker exposure estimates from a high-quality exposure assessment
1-4		Retrospective exposure estimation is an inevitable source of uncertainty in this type of epidemiology study; however, the NIOSH investigators put extensive effort into addressing this issue by developing a state-of-the-art regression model to estimate unknown historical exposure levels using

Page Number	Description of UCC exposure	Description of NIOSH exposure
		variables, such as sterilizer size, for which historical data were available.
3-5	Crude exposure assessment, with a high potential for exposure misclassification	
3-6		… the exposure model and verification procedures are described in Greife et al. (1988) and Hornung et al. (1994). Briefly, a regression model was developed to allow estimation of exposure levels for time periods, facilities, and operations for which industrial hygiene data were unavailable. The data for the model consisted of 2,700 individual time-weighted exposure values for workers' personal breathing zones, acquired from 18 facilities between 1976 and 1985. The data were divided into two sets, one for developing the regression model and the second for testing it. Seven out of 23 independent variables tested for inclusion in the regression model were found to be significant predictors of EtO exposure and were included in the final model. This model predicted 85% of the variation in average EtO exposure levels.
3-7		Good-quality estimates of individual exposure
3-8	"cruder" especially for highest exposure	Based on a validated regression model
4-3 and 4-4	Exposure assessment is much less extensive than that used for the NIOSH cohort, with greater likelihood for exposure misclassification, especially in the earlier time periods when no measurements were available (1925-1973). Exposure estimation for the individual workers was based on a relatively crude exposure matrix that cross-classified three levels of exposure intensity with four time periods. The exposure estimates for 1974-1988 were based on measurements from air sampling at the West Virginia plants since 1976. The exposure	This is in contrast to the NIOSH exposure assessment in which exposure estimates were based on extensive sampling data and regression modeling. In addition, the sterilization processes used by the NIOSH cohort workers were fairly constant historically, unlike chemical production processes, which likely involved much higher and more variable exposure levels in the past.

Page Number	Description of UCC exposure	Description of NIOSH exposure
	estimates for 1957-1973 were based on measurements in a similar plant in Texas. The exposure estimates for 1940-1956 were based loosely on a "rough" estimate reported for chlorohydrin-based EtO production in a Swedish facility in the 1940s (Hogstedt et al., 1979). The exposure estimates for 1925-1939 were further conjectures based on the Swedish 1940s estimate. Thus, for the two earliest time periods (19251939 and 19401956) at least, the exposure estimates are highly uncertain. (See Section A.2.20 of Appendix A for a more detailed discussion of the exposure assessment for the UCC cohort.)	
4-5		It was judged to be substantially superior to the UCC study with respect to a number of key considerations in particular, in order of importance: (1) quality of the exposure estimates …
4-60	largely uninformative in terms of assessing the unit risk estimates derived from the NIOSH study because of the crude exposure assessment used in the UCC study	

The EO IRIS Assessment does not critically evaluate the uncertainties of the NIOSH linear regression model, and does not clarify that the NIOSH model was not validated with any data prior to 1978. In the appendices, similar deficiencies pertain to assertions concerning measures applied purportedly to validate the NIOSH statistical regression model,[32] purported empirical and unbiased bases for the NIOSH statistical regression model,[33] and purportedly unlikely inaccurate characterization of exposure by the NIOSH statistical regression model and its purported validation despite nonexistence of original data upon which it was derived.[34]

NIOSH historical extrapolations of occupational EO exposures prior to the late-1970s, were, as described by Hornung et al. (1994), "derived from a regression model based on

[32] *See* EO IRIS Assessment, Appendix A, at A-14.

[33] *See id.*, Appendix D, at D-75.

[34] *See id.*, Appendix H, at H-27 – H-28.

observed measurements." This regression model was applied to extrapolate worker exposures over a large timespan (1935-1975), during which not a single observed measurement was available to validate the application of that extrapolation procedure, and only a small subset of measures was available during 1976-77. Although the NIOSH statistical regression model reliably estimated exposure measurements made after 1977, Hornung et al. (1994) highlighted that post-1977 regulatory standards and consequent progressively stringent operational EO-exposure controls accounted for the pronounced decreasing trend in measured NIOSH-cohort EO exposures that occurred starting in 1978. Prior to 1978, EO standards and controls were largely or entirely absent. Thus, they were irrelevant to most of the 1935-1975 timespan.

4. **In response to public and SAB comments questioning the lower than expected exposures in earlier years predicted by the statistical regression model, the IRIS Program states that the decrease is related to the sterilizer volume. In other words, the model predicts that smaller sterilizer volume results in lower exposures. This response essentially uses the output of the model to answer a question about whether the model assumptions are correct, instead of independently verifying the validity of these assumptions. This circular reasoning does not address the underlying concern of whether the model assumption that Sterilizer Volume has an inverted parabolic (that is, an upside-down U-shaped) relationship with predicted EO exposure is correct. It also does not address whether other factors that might result in increased exposure during early years were properly accounted for in the model.**

During the review of the 2014 draft EO IRIS Assessment, the SAB questioned the general pattern of historical exposures that were lower in some or all years prior to 1975. The SAB had specifically requested EPA to address this issue in a substantive manner (i.e., using historical, physicochemical, and/or engineering facts or models independent of the NIOSH statistical regression model itself). The SAB noted:

> The SAB is also concerned that public commenters had exposure data from the NIOSH cohort that the EPA did not have. For instance, a few selected graphs were presented in **public comments to the Augmented CAAC that indicated exposure predictions for** four jobs in two of the fourteen plants **showed lower exposures in some or all years prior to 1975. The SAB was provided only a few carefully selected examples, and thus was unable to assess the extent of these surprising data.** This is an uncertainty that can easily be ruled out. **Upon reviewing the model equation in Hornung et al. (1994), the SAB finds the surprising historical behavior to be unlikely** and could be explained by changes

> in processes in specific plants, rather than some failure of the model to capture historically larger exposures. The EPA should ensure that they obtain all relevant data released from NIOSH to members of the public.[35]

Figure 1 above shows that the "surprising historical behavior" characterized by the SAB as "unlikely" does not pertain only to a few specific jobs in different plants, but is a general pattern going back in time prior to the late-1970s. EPA's response to the SAB's concern was:

> contrary to public comments made at the SAB meeting, the NIOSH EtO exposure patterns are not anomalous, but rather reflect the underlying changes in variables predicting exposure over time. One of the principal drivers of the NIOSH exposure levels was the cubic feet of the sterilizers used [see Table III, Hornung et al. (1994)]. It was not uncommon in these plants for sterilizer volume to have increased over time as the demand for EtO-sterilized products increased. **Increased sterilizer volume generally resulted in higher predicted average exposures until the late 1970s, when increased controls were used after it became known that EtO might be dangerous**.[36]

The IRIS Program provided quantitative examples illustrating the point emphasized in the quote above for two different plants, in effect illustrating that the response is consistent with the NIOSH statistical regression model defined in Tables III and VI of Hornung et al. (1994). However, the response is circular and, thus, nonresponsive to the SAB concern, because it relies on the same statistical regression model to attempt to validate its assertion that "increased sterilizer volume generally resulted in higher predicted average exposures until the late 1970s."

The NIOSH regression model predicts that EO exposure levels are proportional to an inverted parabolic (upside-down U-shaped) function of sterilizer volume. This function reaches a maximum predicted EO exposure level at a sterilizer volume value of approximately 4,000 ft^3. This regression function is estimated entirely from measurement data obtained nearly exclusively after 1977. However, NIOSH does not explain a plausible physical basis for this complex exposure/volume relationship observed nearly exclusively after 1977. Although this relationship explains a statistically significant amount of variation in the available EO measures, NIOSH offers no convincing evidence that such a relationship must also reliably apply to periods prior to 1978. Hornung et al. (1994) point out that regulatory constraints, sterilization operation, and

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[35] Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft - August 2014) (Aug. 7, 2015), EPA-SAB-15-012 (2015 SAB Review), at 18 (emphasis added).

[36] EO IRIS Assessment, Appendix I, at I-26 – I-27 (emphasis added).

sterilization technology all differed greatly from prior to 1978 vs. in/after 1978; they emphasize that in 1978, efforts to control EO exposure began to be implemented on an accelerated basis.

None of the three methods applied by Hornung et al. (1994) to validate their statistical regression model[37] is capable of providing any direct form of validation or verification of historical EO exposures actually incurred by the NIOSH cohort. The NIOSH regression model makes that prediction, based on its statistical regression fit to historical EO measurements that only began in the late 1970s, without any other empirical, physical-modeling, or engineering rationale upon which to establish even the plausibility of that model prediction (e.g., based on independent published literature, historical data, physical/compartmental modeling, or any type of reasoning whatsoever bearing on whether sterilizer chamber volume per se is or is not expected to have correlated with or determined historical EO exposure levels prior to the late-1970s).

Hornung et al. (1994) note that pounds of EO used each year served as a surrogate measure of potential EO exposure, but that since such EO utilization data "were not available for all plants in the study, the size of the sterilizer units (in cubic feet of capacity) was substituted after we determined that there was a high degree of correlation between these two variables." However, in order to achieve sterilization efficacy, EO concentrations used in sterilization chambers have remained approximately constant over time—*regardless* of the volume of sterilization chambers used—except insofar as EO concentrations used are well known (and were reported by experienced EO industry workers in interviews discussed below) to have *increased* going backwards in time from the late 1970s, because higher concentrations of EO were used in earlier decades during the evolution of sterilization operations and technology.

Likewise, because utilization of internal sterilization chamber volume has remained fairly constant over time, independent of reduced chamber volume going back in time from the late 1970s, opening of each chamber door and storage of off-gassing sterilized materials resulted in similar immediate concentrations of EO exposure to nearby workers. Reduced chamber volumes going back in time implied that greater numbers of such smaller chambers had to be used to process approximately the same load of sterilized material per plant. To the extent that smaller amounts of sterilized material were processed by plants earlier in time, then those

[37] Hornung et al. (1994) explain that, in the absence of historical exposure data to perform such verification, they applied a three-phase evaluation procedure consisting of 1) a statistical cross-validation procedure applied to a subset of post-1978 empirical measures of EO, 2) comparison of predictions made a by "a panel of 11 industrial hygienists familiar with ethylene oxide levels in the sterilization industry" to the latter subset of empirical data gathered subsequent to 1978, and 3) an evaluation of the ability of the statistical model to explain the empirical variance exhibited by the entire set of empirical measures of (as noted above, nearly all post-1977) EO exposures available for the NIOSH cohort.

processes are certain to have occurred in smaller facilities, implying that going back in time since the late-1970s there was either an increase (as noted above) or no substantial change in the mass-of-EO-used to workspace-volume ratio that determined the time-weighted average EO concentration to which sterilization workers were exposed throughout that period (particularly for the most heavily exposed workers).

Of greater significance, EPA's response does not take into account critical variables, such as level of EO residue in sterilized materials based on the number of air washes used, the length of time sterilized materials were stored prior to return to customers, and where they were stored relative to chamber operations—variables that changed substantially over the decades of EO sterilization prior to the late 1970s. Historical (pre-late-1970s) estimates of NIOSH cohort EO exposure rely on historical extrapolations made only by the NIOSH statistical regression model that were driven primarily by a correlation primarily between chamber volume and post-late-1970s measures of EO exposure. Operational changes that could have influenced EO exposure concentrations prior to 1976/78 were not investigated.

Even the NIOSH study expected higher historical exposures that would be influenced by the absence of engineering and regulatory controls: "Exposure levels are likely to have been higher [than "the late 1970s"], however, before the installation of engineering controls, when the OSHA standard was 50 ppm instead of the present 1 ppm."[38] Moreover, in the 1940s and 1950s, the MAC-TWA and TLV-TWA were 100 ppm.[39] In 1978, the U.S. Food and Drug Administration (FDA) published proposed "maximum residue limits" of 5-250 ppm for medical devices for human use that are sterilized with EO. Prior to 1978, there were no regulatory standards to reduce residues on medical devices, so the residues were around 10–30,000 ppm depending on the type of material.[40] But the IRIS Program failed to take this information into account when modeling the data.

5. The EO IRIS Assessment makes the unsubstantiated claim that "the sterilization processes used by the NIOSH cohort workers were fairly constant historically, unlike chemical production processes, which likely involved much higher and more variable exposure levels in the past."[41] In

[38] Steenland K, Stayner L, Greife A, Halperin W, Hayes R, Hornung R, Nowlin S. 1991. Mortality among workers exposed to ethylene oxide. N Engl J Med, 324(20): 1402-07, at 1406.

[39] ACGIH. 2001. Ethylene Oxide: TLV® Chemical Substances 7th Edition Documentation.

[40] Ernst RR and Whitbourne JE. 1971. Toxic residuals. In the Study of the requirements, preliminary concepts, and feasibility of a new system to process medical/surgical supplies in the field, pp. 46-57, Appendix pp. 1-2, Contract No. DADA17-70-C-0072. U.S. Army Medical R&D Command, Washington, D.C. (Defense Documentation Center Accession No. AD890320 and AD890321).

[41] EO IRIS Assessment, at 4-4.

fact, there was an evolution in technology and practices associated with the sterilization processes between the late 1930s and early 1970s. Data and information from industrial sterilization operators and the literature refute this claim.

Interviews conducted by Exponent, Inc. with three former sterilization operators who began work in the mid-1960s and early to mid-1970s (one was a member of the NIOSH cohort) confirmed operational differences in the sterilization operations in the 1960s and 1970s, and in earlier decades, relative to operations post-1978. This new interview information is supported by information and data in the technical literature on sterilization operations in early decades, including high EO residue levels in and rates of EO off-gassing from EO-sterilized medical materials,[42] and by current quantitative measures of in-chamber EO concentration during sterilization operations after single and multiple air washes that were transmitted to Exponent, Inc. by an industrial sterilization company. These data indicate that the EO IRIS Assessment's assumption that the sterilization processes were fairly constant between the late 1930s and early 1970s is incorrect.

These data also indicate that the variables in the NIOSH model that predicted exposures after the mid-1970s do not capture important potential sources of exposures to sterilizer operators prior to the 1970s:

a. Technology improvements for worker protection such as back venting and use of aeration processing rooms to degas sterilized materials were implemented post 1978. Thus, the presence or absence of back venting or ventilated aeration rooms may help discriminate exposures after 1978, but not between the late 1930s and 1977.

b. Pre-1978 commercial sterilization operations typically included at most only a single post sterilization air wash (relative to numerous washes used typically in later decades); in a current sterilization unit using 100% EO, an EO concentration

[42] Perkins JJ. 1969. Principles and Methods of Sterilization in Health Sciences, 2nd ed. Charles C. Thomas, Springfield, IL; Bruch CW. 1972. Toxicity of ethylene oxide residues. In: Phillips GB, Miller WS, eds. Industrial sterilization, Duke University Press, Durham, NC, at 119-23; Bruch CW. 1981. Ethylene Oxide sterilization—technology and regulation. Industrial ethylene oxide sterilization of medical devices: process design, validation, routine sterilization, AAMI Technological Assessment. Report No. 1-81. Arlington, VA: Association for the Advancement of Medical Instrumentation, at 3-5; Roberts RB, Rendell-Baker L. 1972. Aeration after ethylene oxide sterilisation. Failure of repeated vacuum cycles to influence aeration time after ethylene oxide sterilisation. Anesthesiol, 27(3): 278-82; Stetson JB, Whitbourne JE, Eastman C. 1976. Ethylene oxide degassing of rubber and plastic materials. Anesthesiol, 44(2): 174-80; White JD. 1977. Standard aeration for gas-sterilized plastics. J Hyg Camb, 79: 225-32.

of 17,200 ppm was measured in chamber air after a single wash cycle. Fewer wash cycles result in much higher peak exposures when opening the chamber doors, as well as higher residue levels remaining on the pallets of sterilized material. These higher residue levels contribute to higher exposure levels to those working in areas where pallets are stored.

c. Most 1960s and 1970s operations had evolved to storing the sterilized materials during degassing in a separate room from chamber operations, while operations in earlier decades had chamber operations and sterilized material stored in the same workspace. In the 1950s and 1960s, sterilizer operators would be expected to have higher exposures than in the 1970s because there was one (or no) air washes and the sterilized pallets with high residue levels were often stored in the same room as the chambers.

d. Systematic application of forced and efficient ventilation where sterilizers were operating and where treated pallets were stored was rare or absent prior to the mid-1970s.

e. The period of degassing of sterilized materials was generally about 7 days during the mid-1960s and 1970s, but was ≤1 day in earlier decades. This indicates that the levels of residues in the sterilized materials and, hence, exposures were consistently high in earlier decades.

f. Although with increasing time prior to the mid-1970s sterilization operations involved smaller sterilizers (i.e., having smaller sterilizer chamber volumes), sterilizer operations involved less mechanized or non-mechanized processes, less- or non-ventilated chamber and storage operations, more leaky EO containment during sterilization, and more direct operator exposure to EO vapor (e.g., during change of filters contacting liquid EO and manual connection/disconnection of EO tanks)—factors that likely acted jointly to generate EO exposures to sterilizer operators and other related workers that were greater prior to the late 1970s than during later periods.

g. According to interviewed operators with decades of experience in the EO sterilization industry, concentrations of EO applied in sterilizers currently and since the late 1970s (400–600 mg/L) have been lower by a factor of roughly 1.5 than those applied during earlier decades, and resulting chamber concentrations of EO upon opening of sterilizer chamber doors (which at that time were not actively

ventilated) thus are likely to have been equal to or (with increasing likelihood going back further in time) greater than those that occurred during 1978.

Each of these factors taken alone or in combination indicate that, compared to the sterilization worker environment starting in 1978, when technology improvements and regulatory controls were introduced with increasing frequency and stringency, it is highly probable that greater EO concentrations occurred in the sterilization worker environment from the mid-1960s to the late 1970s. Moreover, it is virtually certain that even greater EO concentrations occurred in the sterilization worker environment prior to the mid-1960s, contrary to trends in occupational exposures during those times that were extrapolated using the NIOSH statistical regression model.

The new information summarized above confirms that the SAB's concern was not effectively addressed by the IRIS Program, and therefore all assessments of EO cancer risk derived using NIOSH epidemiological study data are potentially confounded by greater magnitudes of uncertainty than are stated in the EO IRIS Assessment. These assessments are based on historical extrapolations of occupational exposures prior to the late-1970s produced by the NIOSH regression model and thus necessarily depend on the accuracy and reliability of those extrapolations. This major source of uncertainty in the EO IRIS Assessment is a key defect.

6. **Comparisons of relative reliability made between the NIOSH and UCC studies are inaccurate. These comparisons were a key basis upon which the IRIS Program rejected the UCC Study as a source of epidemiology study data for cancer risk assessment. The EO IRIS Assessment does not acknowledge and appropriately consider limitations of the NIOSH exposure assessment posed by low extrapolations of NIOSH cohort exposures to EO prior to the late 1970s without any corroborating data or any supporting engineering/process considerations derived from or directly relevant to that period of time**.

The EO IRIS Assessment argues inaccurately that the UCC exposure assessment was "too crude" to be used for exposure-response analysis (see Table 1). To the contrary, Greenberg et al. (1990) describe their categorization of departments into "high," "medium," and "low" categories based on a detailed reconstruction of processes using records and interviews of older employees.[43] The categorization was validated using frequencies of visits to the medical department for acute over exposures. The UCC exposure assessment was expanded to include

[43] Greenberg HL, Ott MG, Shore RE. 1990. Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: A mortality study. Br J Ind Med, 47: 221-30.

individual exposure estimates, as described in detail by Swaen et al. (2009).[44] All such efforts associated with epidemiology studies require assumptions and involve uncertainties.

The UCC study, however, includes actual UCC data based on monitoring data from the UCC Texas plant with very similar operations from as early as 1957. Estimates for the 1940-1956 period are based on the published literature for companies using a similar process for EO production. The greatest uncertainty is for 1925-39; however, only 4.8% of the cohort worked during that period. In contrast, **approximately 70% of the NIOSH cohort had workplace exposures prior to 1978, the period of unverified exposure estimates.**

The EO IRIS Assessment's criticism of the UCC approach, i.e., it includes data from a comparable plant that was not part of the cohort, is biased because NIOSH also used exposure data from plants that were not included in the cohort. The fact that UCC-cohort exposures estimated between 1957-1973 are based on contemporary actual exposure measurements obtained from a very similar plant is a major advantage (and certainly not a deficiency) of the UCC approach relative to the NIOSH study.

In contrast, critical limitations and uncertainties associated with NIOSH's statistical regression modeling for the period prior to the late 1970s (based entirely on a fit obtained to data gathered only starting in the late 1970s, since no actual measurements of EO exposure were available for the NIOSH cohort prior to that time) are not accurately characterized or even meaningfully acknowledged in the EO IRIS Assessment or in related NIOSH publications. For example, Hornung et al. (1994) did not reveal that their approach resulted in lower, rather than higher, exposures over the entire period addressed prior to the late 1970s, with no exposures prior to 1978 exceeding those that occurred in and also were reliably estimated for 1978. As noted above, the pattern predicted by the NIOSH statistical regression model conflicts with what is known about early processes in the sterilant industry, and was characterized as "surprising" and "unrealistic" by the SAB.

The EO IRIS Assessment is highly misleading because what it refers to as NIOSH statistical regression model "validation" was done only for its post-late-1970s predictions, since no earlier EO-measurement data were available. Model extrapolations of historical EO exposure prior to the late 1970s were conjectural, relying entirely on putative explanatory power of a regression model fit to EO-measurement data that, as acknowledged by Hornung et al. (1994), exhibited a steeply declining pattern of EO exposures over time post-1977 due to regulatory concerns and EO-control measures that simply did not exist previously. New information

[44] Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM. 2009. Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J Occup Environ Med, 51(6): 714-23.

described above confirms that the NIOSH exposure estimates for periods prior to the late 1970s are substantially and unrealistically low, and therefore are likely to have biased all assessments of EO cancer risk that relied only on NIOSH cohort study data. Moreover, the IRIS Program has failed to investigate whether such bias may render assessments of EO cancer risk unreliable.

7. **The EO IRIS Assessment relies solely on the NIOSH study of sterilant workers and fails to incorporate the important findings from the UCC study of workers in EO producing and using operations. The IRIS Program considered and characterized three factors in its selection of the NIOSH study: cohort size, exposure data, and confounding. Based on these factors, the IRIS Program dismissed the UCC study as a basis for EO cancer risk estimation. In considering cohort size, the IRIS Program ignored the most important comparison—the number of lymphohematopoietic tissue cancers, not the total cohort size.**

As discussed in detail in the other sections, the NIOSH study does not have superior exposure data compared to the UCC study, so both studies have comparable applicability to risk assessment.

Cohort size is only one factor in assessing study informativeness. The most important factor is the number of events of interest, which for a mortality study is dependent on length of follow up and percent deceased. The most recent published study of the UCC cohort reports a sizeable number of deaths due to leukemia and lymphomas, comparable to the events among males in the NIOSH study that would make a meaningful contribution to the number of events for an exposure-response analysis.[45] Despite the smaller number of male workers in the UCC study, they have been followed for a longer period of time (37 yr on average compared to 25 yr for the NIOSH study) and include 51% deceased compared to 19% of the much younger NIOSH sterilant population. The EO IRIS Assessment criticizes the sample size in the UCC cohort, noting (erroneously) "only" 27 LHC cancers and 12 leukemias; the correct number of leukemias is 11 (EPA interchanged the numbers of leukemia and NHL deaths). However, the EO IRIS Assessment does not also note the male population of the NIOSH study had 37 LHC cancers and only 10 leukemias. Furthermore, no substantive criticisms of the NIOSH study appear in the EO IRIS Assessment, when in fact there are major uncertainties with respect to the NIOSH exposure estimates as described in detail above.

The EO IRIS Assessment raises concerns about confounding in the UCC study because of the presence of multiple chemicals in the workplace. This source of bias would only be

[45] Swaen et al. (2009).

expected when analyses yield positive findings, i.e., increases that may not be attributed to EO but to other chemicals. This, in fact, was identified by Greenberg et al. (1990), which reported an increase in leukemia and pancreatic cancer that was found to be attributable to exposures to one or more chemicals in the ethylene chlorohydrin production unit that was characterized as a "low" EO department. The 278 workers involved in that department were removed from the cohort and separately analyzed in a companion publication,[46] which verified increased risk observed by Greenberg et al. (1990). The remaining EO workers did not exhibit cancer increases in subsequent updates.[47] The three central reasons cited in the EO IRIS Assessment for excluding the UCC study are not defensible as explained above, and therefore indicate a biased preference for using the NIOSH study as a sole basis for EO cancer risk estimation.

In addition, the EO IRIS Assessment diminishes the value of the most recent UCC cohort study claiming they were followed so long that background rates of lymphoid tumors would be so large as to miss increased risks due to EO. The important factor is to have sufficient time since first exposure (latency). The 37 yr. average follow-up of Swaen et al. (2003) is not excessive in light of the fact that the most recent hires (1988) have 15 yr. follow-up at most. It is desirable to have 20-25 yr. follow-up for a cancer outcome of interest and even longer when exposures are lower as they were post-1976. Furthermore, there were two earlier studies of this cohort (Greenberg et al., 1990 and Teta et al., 1993) when the cohort was younger, which failed to identify EO-related cancer increases. These studies examined the findings by hire date, duration of exposure, time since first exposure and performed comparisons to the non-exposed chemical workers adjusting for age. It is implausible and speculative that the aging of the cohort masked significant EO-related cancer increases.

The UCC study should have been incorporated in both the hazard characterization and the exposure-response analysis. Consequently, the IRIS Program's handling of these key issues—cohort size, exposure estimation, and confounding—is incomplete, inaccurate, and biased.

8. The use of the supralinear spline model for the lymphoid and breast cancers in the final EO IRIS Assessment is based on an invalid statistical analysis. Because the analysis did not correctly calculate degrees of freedom associated with that fitted model, it contains erroneous measures of absolute and relative goodness of fit of that model. When both the p-values and Akaike

[46] Benson LO, Teta MJ. 1993. Mortality due to pancreatic and lymphopoietic cancers in chlorohydrin production workers. Br J Ind Med, 50: 710-16.

[47] Teta MJ, Benson LO, Vitale JN. 1993. Mortality study of ethylene oxide workers in chemical manufacturing: A 10 year update. Br J Ind Med, 50: 704-09; Swaen et al. (2009).

Information Criterion (AIC) values characterizing fit quality are corrected, the supralinear spline model does not fit the NIOSH lymphoid tumor data statistically significantly better than the log-linear Cox model.

The EO IRIS Assessment justifies why it does not account for the degrees of freedom by citing the 2015 SAB Review: "The knot is preselected and is not considered a parameter in these analyses, consistent with the SAB's concept of parsimony (SAB, 2015)."[48] However, the concept of parsimony is a preference for a simpler model with fewer estimated parameters when fitting and evaluating a single model. The SAB did not direct EPA to violate well founded and widely accepted statistical practice by ignoring the fact that a particular parameter (in this case, the knot of a bi-linear spline model) of a spline model was actually estimated when defining the total number of its estimated parameters, when comparing the goodness of fit of that spline model to another model (such as a log-linear model) that involves no estimated knot.[49]

The EO IRIS Assessment indicates to fit particular supralinear spline models, their "knots were obtained by doing a grid search by increments of 100 ppm x days and then interpolating where appropriate."[50] In other words, the knot of the final supralinear spline model selected was indeed an additional estimated (in this case, numerically optimized) parameter, standard statistical model-fitting procedures always require that p-values be evaluated for a goodness-of-fit statistic only after subtracting one degree of freedom ***for each one of the total number of parameters (a number typically denoted as k) that are estimated when fitting a model***, regardless of how such parameters are estimated.

Failure to follow this procedure always results in an erroneously inflated "p-value" for goodness of fit (only a model with a p-value for goodness-of-fit larger than 0.05 is typically considered acceptable), and thus also in an underestimated value of a corresponding AIC used to compare goodness of fit of different models (a model with a smaller AIC value is preferred, and AIC is defined as twice the sum of k [defined above] and a fit-specific positive quantity). If the proper procedure is not followed to define total degrees of freedom (k), the result is a p-value indicating a fit that is better than actually is the case (i.e., a p-value indicating that deviations between a fitted model and the observed/modeled data are more likely to have occurred by chance alone than actually is the case), and consequently also an AIC value that misrepresents a

[48] EO IRIS Assessment, Appendix D, at D-6.

[49] The EO IRIS Assessment quotes the SAB as follows: "in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example." Appendix D, at D-6, note 11.

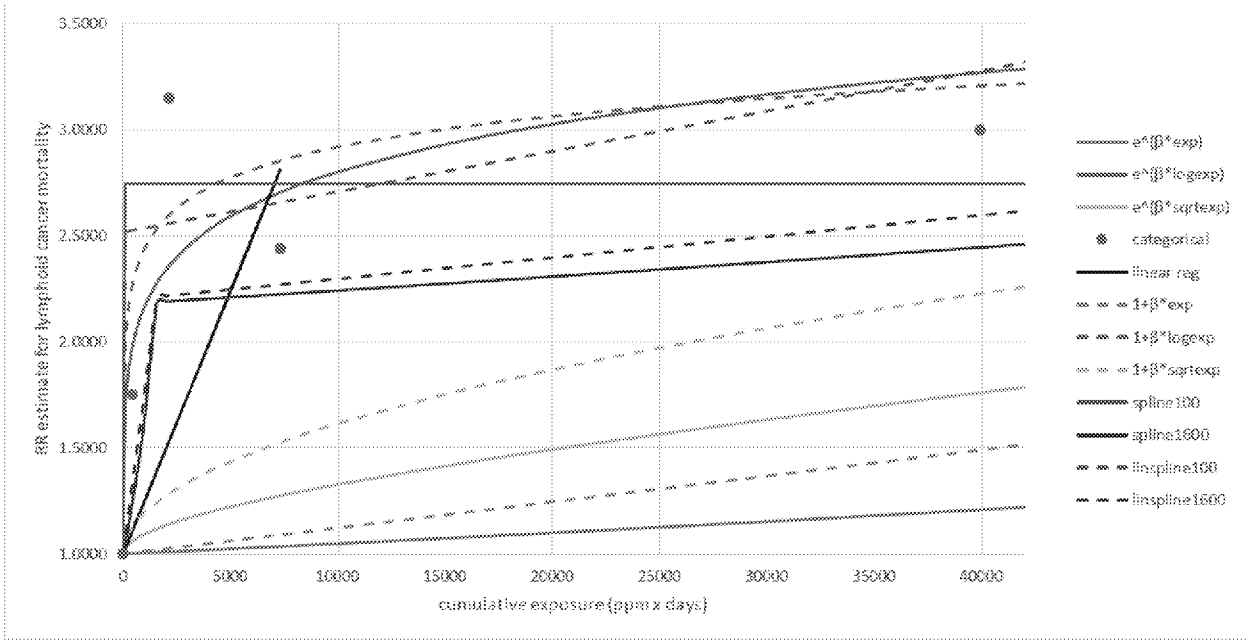
[50] EO IRIS Assessment, Appendix D, Table D-27, note a.

model's goodness of fit relative to that of another model for which degrees of freedom (k) are defined properly.

By ignoring this statistical procedure for its supralinear spline model fit, the EO IRIS Assessment artificially and erroneously inflates the p-value and reduces the AIC value that was used to compare that model to those of other models being compared for which degrees of freedom were defined correctly. **When both the p-values and AIC values are corrected, the selected supralinear spline model does not fit the NIOSH lymphoid tumor data statistically significantly better than the log- linear cumulative model (see Appendix 1).**

9. **The selection of the supralinear spline model for the lymphoid tumors is also based on misleading illustrations of "visual fits" that do not convey either the actual data that were fit or the relative goodness of fit to these data of log-linear and supralinear spline models. Only in a footnote does the IRIS Program acknowledge that the visual comparison misrepresents the log-linear model being compared. Consequently, and erroneously, the fit to the data appears far worse than the supralinear spline model. The data plotted in that figure also were summary data that misrepresent the true magnitude of the scatter of the data that were used for model fitting.**

The EO IRIS Assessment visually represents alternative models considered in relation to data used for model fitting in Figures 4-3 through 4-8, explaining that "to facilitate a visual comparison of the models, select models are replotted against the categorical data in deciles." Figure 4 below reprints Figure 4-3 from the EO IRIS Assessment and illustrates the incorrect basis for the conclusion that the NIOSH exposure-response is supralinear and that only models that are supralinear have good visual fit to the data.



e^(β*exp): RR = $e^{(\beta \times \text{exposure})}$; e^(β*logexp): RR = $e^{(\beta \times \ln(\text{exposure}))}$; e^(β*sqrtexp): RR = $e^{(\beta \times \text{sqrt}(\text{exposure}))}$; categorical: RR = $e^{(\beta \times \text{exposure})}$ with categorical exposures, plotted at the mean cumulative exposure; linear reg: weighted linear regression of categorical results, excluding highest exposure group (see text); 1 + β*exp: RR = 1 + β × exposure; 1 + β*logexp: RR = 1 + β × ln(exposure); 1 + β*sqrtexp: RR = 1 + β × sqrt(exposure); spline100(1,600): Two-piece log-linear spline model with knot at 100 (1,600) ppm × days (see text); linspline100(1,600): Two-piece linear spline model with knot at 100 (1,600) ppm × days (see text). (Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the *y*-axis. They are, however, comparable in terms of general shape.)

Source: Steenland reanalyses for males and females combined; see Appendix D (except for linear regression of categorical results, which was done by EPA).

Figure 4-3. Exposure-response models for lymphoid cancer mortality vs. occupational cumulative exposure (with 15-year lag).

Figure 4. Figure 4-3 from the EO IRIS Assessment using categorical data (solid purple points) to compare the visual fits of the different models, including the selected two-piece log-linear-spline model (dashed red curve) and the standard Cox log-linear regression model (solid blue curve).

Figure 4-3 misrepresents the relative quality of true visual fits to the EO IRIS Assessment's preferred supralinear spline model compared to the more parsimonious log-linear Cox regression model in two important ways. First, Figure 4-3 plots data points that represent categorical data aggregated into quartiles (filled purple points in Figure 4, above) instead of the actual individual cases modeled. This comparison was used in earlier drafts of the IRIS Assessment when the 2014 draft EO IRIS Assessment modeled those categorical aggregated or summary data. However, when the final EO IRIS Assessment followed the SAB's recommendation to model individual cases, the data plots were not corrected accordingly to show the true magnitude of data scatter in relation to fitted models.

Second, the IRIS Program acknowledges in a footnote to Figure 4-3 that "the various models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values (i.e. along the y-axis). They are, however, comparable in terms of general shape." It is not transparent, however, that these graphs cannot be used at all to compare some of the models shown in a valid way. In particular, the lower log-linear model fit shown (the solid blue "line" that appears to go through the origin of the plot shown in Figure 4-3) appears to provide a very poor fit to the cloud of individual data through which that model passes, because the place where that model is shown to intersect the y-axis was artificially forced (in that figure) to intersect the value of 1 along the y-axis, when in fact that model does actually pass centrally through the cloud of actual raw data to which it was fit. That is, although both the EO IRIS Assessment's preferred model and the log-linear model do more or less centrally pass through the cloud of data to which these models were fit, Figure 4-3 misleads the reader by showing a relatively poor fit of the simpler (i.e., more parsimonious) log-linear model compared to the more complex supralinear spline model that was selected in the EO IRIS Assessment.

Figure 5[51] more accurately compares the supralinear spline model (red dashed curve) and the standard Cox log-linear regression model (solid blue curve). The latter model is the approach used by Valdez-Flores et al. (2010) to fit the NIOSH, UCC, and combined NIOSH+UCC study data for lymphoid tumors. In Figure 5, the baseline (zero-exposure) value of hazard rate (HR) to which the log-linear model was fit is set equal to the same baseline HR as that estimated using the supralinear spline model. Therefore, Figure 5 shows more accurately than Figure 4 that the supralinear spline model fits the data no better than standard Cox log-linear regression model.

[51] Figure 5 improves comparison along the y-axis by dividing model-estimated values of hazard rate (HR) ratio by the baseline HR of the individual categorical cases (thus making an apples-to-apples comparison), and uses a logarithmic scale to improve comparison of the linear difference between the fitted models and observed values of relative risk measured as hazard rate ratio (RR). In Figure 4, RR values greater than one appear disproportionally more distant from 1 than RR values less than one, because of the linear RR scale used in that figure. RR values greater than one can be as large as infinity, but RR values less than one cannot be less than 0. In contrast, values of Ln(RR)—i.e., values of RR plotted on a logarithmic scale—as shown in Figure 5 can be as large as infinity and as small as minus infinity (see Appendix 1).

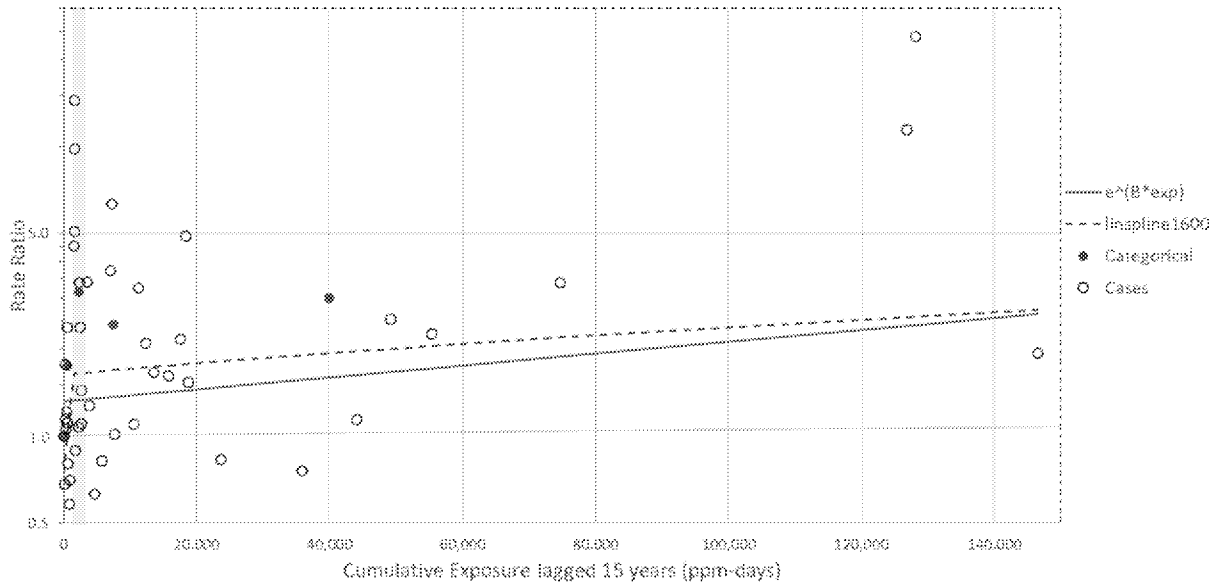


Figure 5. Apples-to-apples comparison of the EO IRIS Assessment's preferred supralinear spline model (red dashed curve) and the log-linear Cox proportional hazards model (solid blue curve), plotted in relation to categorical data (solid purple points) from Figure 4 together with corresponding actual (raw/individual-level) data to which these models were fit (open points).

The misleading plots of categorical data in the EO IRIS Assessment were a key justification for its rejection of the standard Cox log-linear proportional hazards model in favor of a supralinear exposure-response relationship, as indicated in Table 4-14 of the EO IRIS Assessment.

10. The selection of a spline model as the preferred model for EO cancer risk estimation assumes a supralinear increase in tumor response in the low-dose exposure region with a subsequent plateauing of response at higher exposures. The body of cancer epidemiologic studies, including the NIOSH studies, does not support such a pattern of risk. While certain NIOSH sub-analyses suggest increases in male lymphoid tumors and female breast cancers, the findings are limited to the highest cumulative exposure groups, not the lowest.

Steenland et al. (2003) state, "Exposure-response data do suggest an increased risk … for those with higher cumulative exposures to ETO."[52] The authors also say, "The dip in the spline

[52] Steenland K, Whelan E, Deddens J, Stayner L, Ward E. 2003. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control, 14: 531-39.

curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure." The default expectation for a genotoxic carcinogen would be this pattern of monotonically increasing risk in relation to exposure, which is why the authors call it "inconsistent." The EO IRIS Assessment notes that it is not unexpected to have fluctuations in exposure-response curves due to random variation, yet in the exposure-response section the IRIS Program models such plausibly random fluctuation using a supralinear response model.

The EO IRIS Assessment cites Mikoczy et al. (2011)[53] to support the use of the supralinear spline model for breast cancer: "Although the reason for the observed supralinear exposure-response relationship is unknown, it is worth noting that the results of the Swedish sterilizer worker study reported by Mikoczy et al. 2011, …support the general supralinear exposure-response relationship observed in the NIOSH study."[54] However, Mikoczy et al. (2011) studied a low-exposure population that exhibited a significant increase in breast cancer incidence only when analyzed using an internal analysis comparing more-highly exposed to low-exposed workers, and exhibited no such significant increase in a corresponding external analysis involving comparison to matching members of a general population. The explanation for this anomaly lies in the dramatic and (as indicated by Mikoczy et al., 2011) statistically significant deficit of breast cancers in the low exposure group of the internal comparison; because in the internal comparison that low-exposed group was used as the referent group, the two higher exposure groups being compared showed significantly higher rates breast cancer relative to that lower-exposed group.

It might be argued that the non-representative and significantly low rate of breast cancer incidence exhibited by the low-exposure group used for internal comparison simply reflects a Healthy Worker Effect (HWE). However, the breast cancer rate for that group was remarkably low (only about half that of the reference population group of age-matched Swedish women used), and there is no HWE specific to breast (or to any other type of) cancer in Swedish female workers.[55] Thus, the EO IRIS Assessment does not accurately acknowledge and address the problematic nature of the internal-comparison reference group that served as the basis for results of internal comparisons of breast cancer incidence reported by Mikoczy et al. (2011).

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[53] Mikoczy Z, Tinnerberg H, Jonas Björk J, Albin M. 2011. Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: updated cohort study findings 1972–2006. Int J Environ Res Public Health, 8: 2009-19.

[54] EO IRIS Assessment, at 4-71.

[55] Gridley G, Nyren O, Dosemeci M, Moradi T, Adami HO, Carroll L, Zahm SH. 1999. Is there a healthy worker effect for cancer incidence among women in Sweden? Am J Ind Med, 36(1): 193-99.

The EO IRIS Assessment's extra risk estimate suggests a highly potent carcinogen. This is contrary to epidemiology findings which show overall weak positive findings (see Appendix 2). While interest has centered on leukemia, other blood related malignancies, and recently on breast cancer, there are numerous inconsistencies among the studies; elevated risks above background, in isolated studies, are of small magnitude; and there is an absence of a clear exposure-response for any specific cancer type. The most informative studies are the NIOSH (Steenland et al. 2003, 2004) and UCC studies (Swaen et al. 2009), which are studies of comparable utility for risk assessment purposes. These epidemiology studies do not support supralinearity (high risk at low exposures). Certain NIOSH subanalyses showed increase for males only (lymphoid tumors) in the highest (not the lowest) cumulative exposure groups. Extended follow up of chemical workers, UCC and others, and sterilant workers show little, if any, increases. The epidemiological evidence does not support the RSC of 0.1 ppt, which suggests a highly potent carcinogen.

11. The use of a supralinear spline model for cancer risk estimation is inconsistent with the assumed mode-of-action of EO toxicity and tumorigenicity. Such a model predicts higher risk at low exposures compared to risks predicted at higher exposures, which is contradicted by the well-understood mode of action of EO in experimental animals and humans as described in the EO IRIS Assessment. Thus, the EO IRIS Assessment relies on human cancer risk estimates based on spline-model dose-response extrapolations that are internally inconsistent with its own evaluation of the mode of action of EO. The mean air concentration equivalent to the endogenous concentration in non-smoking humans with no known EO exposures is 1.9 ppb (range 0.13-6.9 ppb; continuous), which is 19,000 times greater than the EO IRIS RSC of 0.1 ppt. An alternative LEC (1/million) of 0.5-1.2 ppb is a more pragmatic, science-based approach for EO risk assessment.

As a direct acting DNA- and protein-reactive toxicant, the high-level toxicological and cancer mode of action of EO importantly predicts a *sublinear* increase in dose-response at low exposures and an associated dose-disproportionate *increase* in toxicity at higher EO doses.[56] This expected dose-response pattern is due to attenuation of low-dose EO toxicity mediated by intervention of key detoxification pathways (EO conjugation with glutathione and enzymatic hydrolysis to oxidized metabolites; repair of EO-induced DNA adducts), and an associated dose-disproportionate (supralinear) increase in toxicity at higher doses due to saturation of those same pathway(s) as the EO dose increases, as summarized below in Figure 6.

[56] Kirman and Hays (2017).

The EO IRIS Assessment describes and supports this projected EO mode of action and its implications for the shape of the cancer dose response in the low- to high-dose regions as follows:

> [E]PA considers it *highly plausible that the dose-response relationship over the endogenous range is sublinear* (e.g., that the baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work more effectively for lower levels of endogenous adducts), that is, that the *slope of the dose-response relationship for risk per adduct would increase* as the level of endogenous adducts increases.[57]

The EO IRIS Assessment's analysis of the EO mode of action emphasizes that the dose-response is highly likely ("highly plausible") to be *sublinear* "over the endogenous range" of internal EO doses that result from well-characterized endogenous production of EO secondary to metabolism of ethylene originating from normal biological processes.

Exploiting the well-defined linear relationship between exogenous EO exposure and systemic hemoglobin adducts in humans, Kirman and Hays (2017) estimate that the contribution of endogenously generated EO exposures to the overall systemic dose of EO is substantially greater than the 0.1 ppt exogenous EO exposure projected by the EO IRIS Assessment as resulting in a 1×10^{-6} cancer risk in humans. A meta-analysis of 661 non-smoking individuals not exposed to external EO indicated that endogenous background EO exposures are equivalent to a mean external exogenous EO exposure of 1.9 ppb (range 0.13-6.9 ppb). This "endogenous equivalent" contribution to the overall systemic EO dose is 19,000 times greater than the 0.1 ppt exogenous EO one-in-a-million risk dose estimated by the EO IRIS Assessment.

It is clear that even a 1000-fold increase in exogenous EO exposures above 0.1 ppt would only approach the low end of the total systemic EO dose contributed by endogenous EO generation. Any contributions of exogenous EO to cancer risk below this low-end endogenous dose would not be detectable within the likely day-by-day intra- and inter-individual variability (0.13-6.9 ppb) associated with normal endogenous EO exposure loads.

[57] EO IRIS Assessment, at 4-95 (emphasis added).

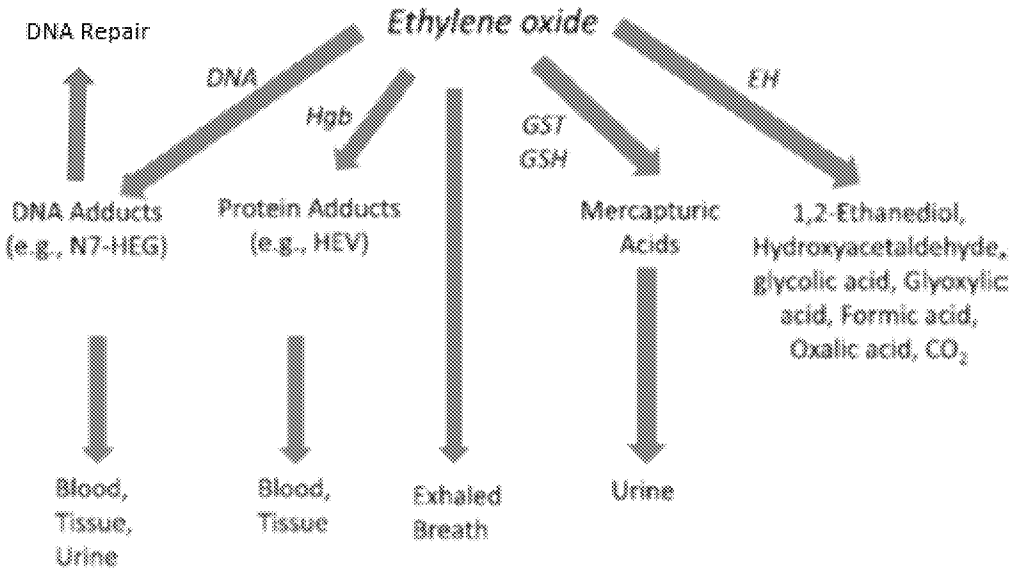

Figure 6. EO metabolism (adapted from Kirman and Hays, 2017).

Kirman and Hays (2017) also recognize that increased EO hemoglobin adducts associated with smoking provided an opportunity to further check the EO IRIS Assessment's supralinear model predictions that moderately low external EO exposures realistically contribute to increased cancer risks. A meta-analysis of 379 smokers not otherwise exposed to EO found that smoking increased EO exposures approximately 10-fold above the endogenous equivalent dose for background (non-EO exposed) individuals (mean background endogenous equivalent exposure = 1.9 ppb; mean smoker exposure = 18.8 ppb). The spline-model relied on by the EO IRIS Assessment predicts that the moderate increase in EO exposure associated with smoking would result in a detectable increase in lymphohematopoietic and breast cancers. However, this expectation is not met despite the very large smoking cohort.

Kirman and Hays (2017) note that smoking has been causally associated only with one subtype of lymphohematopoietic cancer, acute myeloid leukemia (AML). Not only is this cancer not increased in the NIOSH occupational cohort specifically exposed to higher doses of EO than those resulting from smoking, but Valdez-Flores et al. (2010), using a non-spline-based risk model, also demonstrate a statistically significant negative slope between cumulative exposure to EO and AML in that same NIOSH cohort. Kirman and Hays (2017) also observe that evidence

of a causal relationship between smoking and breast cancer is considered only as suggestive and not sufficient. Thus, projections of low-dose elevations in specific EO-associated cancer risks based on spline model extrapolations from relatively high occupationally-exposed individuals are not consistent with cancer outcomes in the much larger smoking cohort experiencing moderately elevated EO exposures.

Kirman and Hays (2017) also address the concern that any additional exogenous EO exposures above background, regardless of how small, represent a plausible contribution to increased cancer risks. They conclude that the approximate four order of magnitude disparity between EO endogenous exposures (mean = 1.9 ppb) and EPA projected increased risk at exposures greater than 0.1 ppt "creates a signal-to-noise issue [in the biological plausibility of tumor outcomes] when exogenous exposures fall well below those consistent with endogenous exposures. In such cases, small exogenous exposures may not contribute to total exposure or to potential effects in a biologically meaningful way."

Recently, Calabrese (2018)[58] offers additional insight into the lack of plausibility of additivity to background of risks associated with low (and particularly less than background) exposures to EO. Calabrese reports that the mutational spectra of K-ras in EO-induced lung and Harderian gland tumors, and H-ras and p53 in mouse mammary tumors, were not at all similar to mutational spectra of these same tumors in control mice from the EO studies. These molecular-level data indicate that the mode of action of generation of control (background) tumors differs substantively from those originating from exogenous EO-exposed animals, even though control animals experience significant endogenous EO exposures. Thus, these data stand in contrast to the assumption of additivity to background that presumes that chemically-induced elevation of background tumors that are otherwise pathologically similar to chemically-induced tumors must share common mode(s) of action reviewed by Calabrese (2018).

The potential for additivity to background also is not supported by a comparison of total endogenous EO-specific DNA adducts in spleen, liver and stomach of rats relative to adducts in these same tissues resulting from a thousand-fold range of EO intraperitoneal doses (0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05 and 0.1 mg/kg/day; 0.1 mg/kg/day approximately equivalent to a 1 ppm 6 hr/day EO inhalation exposure).[59] Importantly, Marsden et al. (2009) also emphasize that the increase in adducts associated with exogenous EO were not statistically significant at any

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[58] Calabrese EJ. 2018. The additive to background assumption in cancer risk assessment: A reappraisal. Envir Res, 16: 175-204.

[59] Marsden DA, Jones DJ, Britton RG, Ognibene T, Ubick E, Johnson GE, Farmer PB, Brown K. 2009. Dose-response relationships for N7-(2-hydroxyethyl)guanine induced by low-dose [^{14}C]ethylene oxide: evidence for a novel mechanism of endogenous adduct formation. Cancer Res, 69(7): 3052-59.

dose with the exception of adducts in liver in rats administered 0.05 mg/kg/day, suggesting that exogenous adducts may not present any additional risk over endogenous adducts over this range of EO doses (i.e., additivity to background). Interestingly, endogenous DNA adducts were statistically increased in spleen and liver at the 0.05 and 0.1 mg/kg/day EO, indicating that higher EO doses alter internal biological processes leading to increased potential for endogenous EO formation.

Further investigations demonstrated that the high-dose-specific in endogenous-only adducts may have been secondary to increased oxidative stress. Both the high level of background endogenous adducts and high-dose specific increases in endogenous-only EO adducts further supports the authors' conclusion that "if the compound [EO] is produced endogenously, low doses of exogenous exposure may be overwhelmed by the background levels, leading to no detectable statistically significant increase in risk due to the external exposure." This conclusion (see Figure 6) is entirely consistent with the analyses developed by Kirman and Hays (2017) in which endogenous EO equivalent exposures in humans (mean = 1.9 ppb) are estimated as being 19,000 times higher than the exogenous EO dose of 0.1 ppt presenting a one-in-a-million cancer risk from spline-model low-dose extrapolation.

An alternative LEC (1/million) of 0.5-1.2 ppb is within the range of endogenous EO levels. Taking into account the biological mode of action and the endogenous EO equivalent exposures in humans, this approach is more plausible and science-based than the EO IRIS assessment.

12. The statistical, epidemiological and biological evidence does not support the selection of supralinear spline models to fit the NIOSH study data in the EO IRIS Assessment. A more scientifically sound conservative alternative is to use the Valdez-Flores et al. (2010) approach, which incorporates all the available data from the two strongest human studies (NIOSH and UCC). This approach has been adopted by the Scientific Committee on Occupational Exposure Limits.

As described in previous sections, the selection of the supralinear spline model is based on incorrect statistical analysis and biased evaluation of the NIOSH exposure modeling relative to the UCC exposure estimates. Furthermore, the epidemiological evidence and biological mode of action do not support the supralinear spline model. A more scientifically supportable approach is that published by Valdez-Flores et al. (2010), who make full use of the available data from both the NIOSH and UCC cohorts. The effect was modeled as a standard Cox proportional log-linear hazards model (i.e., exponentiated linear) function of cumulative EO exposure (ppm-days) treated as a continuous variable.

The EO IRIS Assessment focuses the cancer risk assessment on lymphoid tumors (defined by NIOSH as including non-Hodgkin's lymphoma, lymphocytic leukemia and multiple myeloma) and breast cancer incidence. The weight of evidence does not support breast cancer as an endpoint for risk assessment (see Appendix 2). Therefore, our analysis focuses on the mortality data for lymphohematopoietic (LH) tissue cancers including leukemia (and specific myeloid and lymphocytic leukemia), non Hodgkin's lymphoma (NHL), multiple myeloma (MM) and "lymphoid" cancers (a grouping developed in Steenland et al. (2004) that included NHL, MM, and lymphocytic leukemia).

Valdez-Flores et al. (2010) propose a range of 1-3 ppb based on the Maximum Likelihood Estimate (MLE) of the Effective Concentrations (ECs) associated with an extra risk of one-in-a-million [EC(1/million)] (see Table 2).[60] The authors select the MLE as the most reliable data for point of departure because the Lowest Effective Concentrations LECs), the 95% lower bound on the ECs, are insensitive to the magnitude of the best estimated slope, which can be negative, yet have a positive 95% upper confidence limit resulting in a finite LEC as occurred for multiple myeloma.

Table 2: Maximum Likelihood Estimate (MLE) of the EC (1/million) and Lowest Effective Concentration (LEC)

EO type of cancer (mortality)	MLE UCC & NIOSH (ppb)	LEC UCC & NIOSH (ppb)	LEC NIOSH only (ppb)
Lymphoid	1.5	0.5	0.2
Non-Hodgkin's lymphoma	2.3	0.9	0.8
Multiple Myeloma	Negative slope, value not calculated	1.2	0.8
Leukemia	9.2	0.9	0.9
Lymphocytic Leukemia	2.4	0.9	0.9
Breast cancer	0.7	0.1	0.1

[60] NIOSH only provided ACC with the breast cancer mortality and not the incidence data, despite multiple requests for the incidence data. The results from the breast cancer mortality are included in Table 2 for completeness.

EO type of cancer (mortality)	MLE UCC & NIOSH (ppb)	LEC UCC & NIOSH (ppb)	LEC NIOSH only (ppb)
Range for LHC	1.5-9.2	0.5-1.2	0.4-0.9
Range for LHC and breast cancer	0.7-9.2	0.1-1.2	0.1-0.9

The MLE and LEC values reported in Table 2 are conservative values because (a) extra risk was calculated despite no statistically significant slope in the exposure-response analyses; (b) the NIOSH data was included without adjustment for likelihood of underestimation of exposures; and (c) the limited evidence of cancer risk based on the entire body of epidemiologic evidence (summarized in Appendix 2).

The EO IRIS Assessment and Valdez-Flores et al. (2010) identify several differences between the two approaches in deriving their recommended 1/million exposure levels to use as points of departure (see Table 3).[61]

Table 3: Approximate sources of differences between Valdez-Flores et al. (2010) and EO IRIS Assessment approaches

Valdez-Flores et al (2010) compared to EO IRIS Assessment	Reference	Factor
Extra risk at age 70 instead of 85 years	Valdez-Flores et al. (2010), p. 319	2.3
Different approaches to implementing age-adjusted adjustment factor (ADAF)	Valdez-Flores et al. (2010), p. 319 used an approach that adjusted the slope; EPA's cancer risk assessment guidelines (2005) use 1.66	1.66
Use of incidence background rates compared to mortality background rates in lymphoid tumor unit risk estimation (incidence/mortality ratio, $R_{i/m}$).	$R_{i/m}$ = 5.26/1.99 The EO IRIS Assessment unit risk using background lymphoid cancer incidence rates with model for lymphoid mortality data = 5.26/ppm, and unit risk using background	2.64

[61] *See* EO IRIS Assessment, Appendix A, at A-33 – A-35.

	mortality rates with model for lymphoid mortality data is 1.99/ppm; see Table 4-7, page 4-23; whereas Valdez-Flores et al. (2010) unit risk using background lymphoid mortality rates with model for lymphoid mortality data	

Valdez-Flores et al (2010) used well-accepted statistical principles to guide decisions about whether to include a lag period, how to calculate the degrees of freedom, and whether the MLE for the EC (1/million) can be interpolated within the lower region of the experimental data set. For example, because there was no significance between the models with and without a lag period and no clear biological plausibility for selection of a specific lag period, the more parsimonious model (no lag) was selected. In contrast, the IRIS Program tested different lag periods and knots but did not fully account for the higher degrees of freedom typically considered when different ranges of values are tested.

Valdez-Flores et al. (2010) also modeled down to 10^{-6} risk, whereas the IRIS Program modeled to 10^{-2} risk and used the LEC01 as a point of departure (POD) for linear low-dose extrapolation. Valdez-Flores et al. (2010) suggest that PODs should be within the range of observed exposures, and chose a 10^{-6} risk level because the corresponding exposure level was in the range of the observed occupational exposures (converted to equivalent environmental exposures). Thus, Valdez-Flores et al. (2010) fully used the experimental data to derive a 10^{-6} risk level.

An additional difference that is not captured in Table 3 is the EO IRIS Assessment estimates risk for both lymphoid and breast cancer, whereas Valdez-Flores et al. (2010) estimates risk for lymphoid tumors alone. As discussed above and in greater detail in Appendix 2, breast cancer is not a target of EO. The EO IRIS Assessment recognizes that magnitudes of increased risks for breast cancer were not large and implies that the evidence is weaker than that for lymphoid tumors. Despite these issues, the EO IRIS Assessment introduces breast cancer as a target organ and inappropriately develops a risk value. Uncertainties described by Steenland et al. (2003) related to the breast cancer incidence study are dismissed as unimportant. It is notable that the ratio between risk for lymphoid plus breast cancer incidence (6.06 per ppm)[62] divided by the risk for lymphoid tumor incidence alone (5.26 per ppm)[63] is only 1.15.

[62] EO IRIS Assessment, at 4-58.

[63] *Id.* at 4-31.

As discussed above, the NIOSH exposure assessment was not validated prior to the late 1970s and likely underestimated exposures. In contrast, the UCC exposure estimation from the 1940s to 1970s was based on actual data from similar operations during the same time period.[64] The greatest uncertainty is between 1925-1939, but only 4.8% of the UCC cohort had work history before 1940.[65] These uncertainties are no greater than the NIOSH study uncertainties and do not justify study rejection for exposure-response analysis. Both studies are well-conducted epidemiology studies with comparable power in terms of number of events for males and of comparable utility in terms of individual exposure estimates. In fact, the UCC study was originally a NIOSH study, in that it was nested within a NIOSH/UCC collaborative study of 29,000 UCC workers in the Kanawha Valley of West Virginia.[66]

The EO IRIS Assessment also criticizes Valdez-Flores et al. (2010) for not using any log cumulative exposure models which were found to be statistically significant in analyses by Steenland et al. (2004), consistent with the apparent supralinearity of the NIOSH exposure-response data. Yet, the EO IRIS Assessment also considers the log cumulative exposure model to be "problematic because this model, which is intended to fit the full range of occupational exposures in the study, is inherently supralinear …, with the slope approaching infinity as exposures decrease towards zero, and results can be unstable for low exposures."[67]

Similarly, the IRIS Program rejected other statistically significant models due to unstable results for low exposures. As noted above, the assumption of supralinearity is based on a flawed statistical analysis of its preferred-model fit and on a misleading visual comparison of invalidly overlaid models plotted in relation to categorical data grouped in quartiles instead of considering the pattern of RR for individual cases, which more realistically reveals a very noisy data cloud through which the simpler and traditionally accepted Cox proportional model fits as well as the supralinear spline model.

Crump (2005) noted that:

> Because of these potential distortions of the exposure-response shape, one should be cautious in drawing conclusions about the shape of the exposure response from epidemiological data. Since even random, unbiased errors in exposure measurement will convert a linear exposure response, and can convert sub-linear

[64] Swaen et al. (2009).

[65] *Id.*

[66] Rinsky RA, Ott G, Ward E, Greenberg H, Halperin W, Leet T. 1988. Study of mortality among chemical workers in the Kanawha Valley of West Virginia. Am J Ind Med, 13: 429-38.

[67] EO IRIS Assessment, at 4-10.

> response, into a seemingly supralinear shape, one should be particular[ly] cautious about concluding an exposure-response is truly supralinear. In particular, it could be inadvisable to extrapolate an observed supralinear exposure response to low exposures to predict human risk.[68]

Crump's caution is especially relevant to the NIOSH data in light of the high potential for exposure misclassification in the earlier years of the NIOSH study when there was no data to validate the NIOSH exposure model, as described above. EPA's cancer risk assessment guidelines echo this caution: "a steep slope [i.e., supralinear] also indicates that errors in an exposure assessment can lead to large errors in estimating risk."[69]

D. Conclusion

The 2014 NATA fails to meet the requirements of the IQA and the OMB and EPA Guidelines because its use of the EO IRIS Assessment is not the best available science. Therefore, the 2014 NATA risk estimates for EO should be withdrawn and corrected to reflect scientifically-supportable risk values and EPA should not use the EO IRIS Assessment's inhalation RSC of 0.1 ppt to calculate EO risk in its ongoing CAA Section 112 RTR rulemakings and other regulatory actions. As discussed above, a more reasonable and scientifically supportable approach to an exposure response analysis yields ranges for the MLE (1.5-9.2 ppb) and LEC (0.5-1.2 ppb) that are more than three orders of magnitude greater than the EO IRIS Assessment's environmental concentration associated with one-in-a-million risk.

Sincerely,

William Gulledge

William P. Gulledge
Senior Director
Chemical Products & Technology Division

Enclosures:

Appendix 1 – Statistical Issues with EPA's Calculation of p-values and AIC's for Spline Models and Linear Models in the EO IRIS 2016
Appendix 2 – Brief Summary of Epidemiological Data for EO

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[68] Crump KS. 2005. The effect of random error in exposure measurement upon the shape of the exposure response. Dose-Response, 3: 456-64.

[69] EPA, Guidelines for Carcinogen Risk Assessment, at 3-19.

Appendix 1

Statistical Issues with EPA's Calculation of p-values and AIC's for Spline Models and Linear Models in the EO IRIS 2016

Ciriaco Valdez-Flores, Ph.D., P.E.
Professor of Practice
4073 Emerging Technologies Building
3131 TAMU
College Station, TX 77843-3131
Tel. (979) 458-2366 Fax: (979) 458-4299
e-mail: ciriacov@tamu.edu

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Introduction

The document "Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8) In Support of Summary Information on the Integrated Risk Information System (IRIS), December 2016" (EO IRIS 2016) has several statistical inaccuracies that play an important role in model selection and, ultimately, in the risk assessment of EtO. The exposure-response modeling of lymphoid mortality for the NIOSH study is reviewed here, and statistical pitfalls are highlighted. EPA's statistical numbers are corrected herein and new results are derived. These corrected results question conclusions drawn by EPA about model selection. Although EPA's conclusions for the other endpoints are not analyzed herein, similar statistical pitfalls must have been incurred, as the statistical pitfalls are related to the methodology that was used for all endpoints analyzed by EPA.

Table 1 reproduces Table 4-6 of EO IRIS 2016. In this table EPA to summarizes how the linear spline model with knot at 1600 ppm × days was selected to describe the relationship between lymphoid mortality rate ratio and cumulative exposures to EO. The summary in the table indicates that the model was selected because: a) adequate statistical fit; b) adequate visual fit; c) including local fit (visual) to low-exposure range; linear fit; and d) AIC within two units of lowest AIC models considered.

It can also be shown (using the likelihood ratio test -- analyses not presented here) that EPA's selected linear spline model does not fit the NIOSH lymphoid mortality data statistically significantly better (at the 5% significance level) than the nested linear model. Similarly, log-linear spline model with knot at 1600 ppm-days does not fit the NIOSH lymphoid mortality data statistically significantly better (at the 5% significance level) than the nested log-linear model. Thus, according to the following SAB recommendation on page 12, the log-linear and the linear models should be preferred over the log-linear spline and linear spline models, respectively:

> Third, the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered. Attention to this principle becomes even more important as the information in the analysis dataset becomes even more limited.

Thus, models with very few estimated parameters should be favored in cases where there are only a few events in the dataset.

Table 1. The following table has been extracted from EO IRIS 2016 Table 4-6

Table 4–6. Models considered for modeling the exposure-response data for lymphoid cancer mortality in both sexes in the National Institute for Occupational Safety and Health cohort for the derivation of unit risk estimates

Model[a]	*p-value*[b]	AIC[c]	Comments
Two-piece spline models			
Linear spline model with knot at 1,600 ppm × days	0.07	462.1	**SELECTED.** Adequate statistical and visual fit, including local fit to low-exposure range; linear model; AIC within two units of lowest AIC of models considered.
Linear spline model with knot at 100 ppm × days	0.046	461.4	Good overall statistical fit and lowest AIC of two-piece spline models, but poor local fit to the low-exposure region, with no cases below the knot.
Log-linear spline model with knot at 1,600 ppm × days	0.07	462.6	Linear model preferred to log-linear (see text above).
Log-linear spline model with knot at 100 ppm × days	0.047	461.8	Good overall statistical fit and tied for lowest AIC[c] of two-piece spline models, but poor local fit to the low-exposure region, with no cases below the knot.
Linear (ERR) models (RR = 1 + β × exposure)			
Linear model	0.13	463.2	Not statistically significant overall fit and poor visual fit.
Linear model with log cumulative exposure	0.02	460.2	Good overall statistical fit, but poor local fit to the low-exposure region.
Linear model with square-root transformation of cumulative exposure	0.053	461.8	Borderline statistical fit, but poor local fit to the low-exposure region.
Log-linear (Cox regression) models (RR = $e^{\beta \times \text{exposure}}$)			
Log-linear model (standard Cox regression model)	0.22	464.4	Not statistically significant overall fit and poor visual fit.
Log-linear model with log cumulative exposure	0.02	460.4	Good overall statistical fit; lowest AIC[c] of models considered; low-exposure slope becomes increasingly steep as exposures decrease, and large unit risk estimates can result; preference given to the two-piece spline models because they have a better ability to provide a good local fit to the low-exposure range.
Log-linear model with square-root transformation of cumulative exposure	0.08	462.8	Not statistically significant overall fit and poor visual fit.

[a]All with cumulative exposure as the exposure variable, except where noted, and with a 15-yr lag.

[b]*p*-values from likelihood ratio test, except for linear regression of categorical results, where Wald *p*-values are reported. $p < 0.05$ considered "good" statistical fit; $0.05 < p < 0.10$ considered "adequate" statistical fit if significant exposure-response relationships have already been established with similar models.

[c]AICs for linear models are directly comparable and AICs for log-linear models are directly comparable. However, for the lymphoid cancer data, SAS proc NLP consistently yielded −2LLs and AICs about 0.4 units lower than proc PHREG for the same models, including the null model, presumably for computational processing reasons, and proc NLP was used for the linear RR models. Thus, AICs for linear models are equivalent to AICs about 0.4 units higher for log-linear models. No AIC was calculated for the linear regression of categorical results.

EPA's Misinterpretation of SAB Comments about the Knot of Spline Models

EPA justifies the p-values and AIC values for the linear spline and log-linear spline models in their Table 4-6 misquoting SAB's comments. In section D.3.2 of the appendices (reference), EPA states (emphasis added) "Table D-27 also presents the AIC values for the same models to facilitate comparison with the two-piece spline models, which include an extra parameter. [The knot is preselected and is not considered a parameter in these analyses, consistent with the SAB's concept of parsimony (SAB, 2015)].[14]" Their footnote 14 in the same sections states "[14] in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example" [page 12 of SAB (2015)]."

Although the SAB quote is accurate, the quote just a fragment of a response and is taken out of context. The full question and SAB response are as follows (emphasis added):

> *2b: For the (low-exposure) unit risk estimates, EPA presents an estimate from the preferred model as well as a range of estimates from models considered "reasonable" for that purpose (Sections 4.1.2.3 and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the "reasonable models" is clearly and transparently described and scientifically appropriate.*
>
> The SAB understands that the EPA considered four "reasonable" models for providing unit risk estimates; these all have unit risk estimates reported in Table 4-13. A few additional models are described in Tables 4-12 and 4-13, some of which could also be considered reasonable. The presentation of "reasonable" models considers model fit and some a priori (but not clearly articulated) notion about the acceptable shape of the dose-response function in the low-dose region. Because the data do not appear to conform to the a priori notion, the draft assessment also considers models based on an untransformed continuous exposure term or a linear regression of the categorical results as reasonable. However, these models do a poorer job reflecting the patterns in the data. Although much of the approach is scientifically appropriate, the SAB does not agree with all of the judgments. In order to strengthen the assessment and presentation, some modifications are suggested to the approach for comparing models and choosing which models are reasonable. The SAB recommends that

the discussion be revised to provide more clarity and transparency as well as making the disposition easier to follow. In general, discussion of statistical significance should occur in a more nuanced fashion so that important perspective about the results is not lost in the tendency to turn the statistical evidence into a binary categorization of significant vs. not significant. (This can mislead readers into interpreting a pair of results as inconsistent when their p-values, effect estimates, and 95% confidence intervals are very similar, but the two p-values happen to be on opposite sides of 0.05.) Consideration of reasonable models should address the quality of fit in the region of interest for risk assessment. Prioritizing sufficiently flexible exposure parameterizations (e.g., not linear) and exposure functions with more local behavior (e.g., splines, linear and cubic) reduces the impact of highly exposed individuals on the risk estimates for lower exposures. Discarding a model because the fitted curve is "too steep" needs scientific justification. Furthermore, follow-up by the EPA is needed to clearly articulate the criteria for determining that models are reasonable as well as providing transparent definitions for frequently used terms such as "too steep," "unstable," "problematic," and "credible" (p. 4-38). The SAB recommends assigning weight to certain types of models based on a modified combination of biologic plausibility and statistical considerations, and using somewhat different considerations for comparing AICs than those currently employed in the draft assessment.

Regarding statistical considerations about various models, the SAB recommends a different set of emphases in the priorities for the most reasonable models and gives guidance on the preference for their ordering. First, priority should be given to regression models that directly use individual-level exposure data. Because the NIOSH cohort has rich individual-level exposure data, linear regression of the categorical results should be de-emphasized in favor of models that directly fit individual-level exposure data. Second, among models fit to individual-level exposure data, models that are more tuned to local behavior in the data should be relied on more heavily. Thus, spline models should be given higher priority over transformations of the exposure. Third, the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered. Attention to this principle becomes even more important as the information in the analysis dataset becomes even more limited. Thus, models with very few estimated parameters should be favored in cases where there are only a few events in the dataset. To elaborate further, in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one

such example. Use of AIC can assist with adhering to this principle of parsimony, but its application cannot be used naïvely and without also including scientific considerations. (See further discussion below.) Beyond these recommendations for choosing among models, one advantage of fitting and examining a wide range of models is to get a better understanding of the behavior of the data in the exposure regions of interest. For instance, the models shown in Table 4-13 and Figures 4-5 and 4-6 can be compared, ideally with one or more of these presentations augmented with a few more model fits, including the square root transformation of cumulative exposure, linear regression of categorical results given more categories, and several additional 2-piece linear spline models with different knots. From the comparisons, it is clear that these data suggest a general pattern of the risk rising very rapidly for low-dose exposures and then continuing to rise much more slowly for higher exposures. It is reassuring to observe that many of the fitted models reflect this pattern even though they have different sensitivity to local data.

Results of statistical analyses do not always conform to an a priori understanding of biologic plausibility. When this is the case, investigators need to reassess whether the data are correct, a different approach to model fitting should be employed, or whether the prevailing notion of biologic plausibility should be re-examined. When sufficient exploration of the fitted models has been conducted and a range of models with different properties all suggest a dose-response relationship that would not have been predicted in advance (as is the case in these NIOSH data analyses), then the remaining two considerations should be reviewed. The response to Charge Question 4 further discusses uncertainty in the exposure data. The SAB also encourages finding opportunities to use other evidence from the literature to support the observed dose-response relationship. Specifically, the SAB encourages a discussion of the Swedish sterilization workers study results using the internal comparison group.

The application of AIC for selecting models is acceptable within some constraints as outlined in the following discussion. Burnham and Anderson (2004) is an additional reference that discusses the use of AIC for model selection. (The following discussion is intended to be fairly comprehensive and thus covers points that the SAB did not identify as problematic in the draft assessment.) AIC is an appropriate tool to use for model selection for both nested and non-nested models, provided these models use the same likelihood formulation and the same data. AIC is not the preferred way to characterize model fit. For model selection, (1) AIC is not an appropriate tool for comparing across different models that are fit using different measures, such as comparing a Poisson vs. least squares fit to count data; (2) one should not use AICs to compare models using different

transformations of the outcome variable; and (3) comparing AICs from models estimated using different software tools, including different implementations within the same statistical package can be challenging because many calculations of AIC remove constants in the likelihood from the estimated AIC. These AIC features require that users interested in comparing AICs across different software routines (even those within one statistical package) understand exactly what likelihood is being maximized and how the AIC is calculated. AIC can be used to compare the same regression model with the same outcome variable and different predictors whether or not these models are nested. This gives a consistent estimate of the mean-squared prediction error (MSPE), which is one criterion for choosing a model. Finally, the theory behind this MSPE criterion can break down with a large number of models. Thus, naïve applications of AIC for model selection can be problematic (but are not necessarily so in any particular application). In particular, differences in AICs could be an artifact of how the calculation was done. This is a possible difference between the linear and exponential relative risk models applied to the breast cancer incidence data. Although the EPA provided some clarification about its approach in its February 19, 2015 memo to the SAB, the SAB still does not have sufficient information to determine whether or not this is the case.

In conclusion, although the SAB concurs with the EPA's selected model, it believes that aspects of EPA's approach to model selection can be refined and that more transparency in the presentation is needed.

Summary of recommendations:

- Revise the discussion to provide more clarity and transparency as well as making the disposition easier to follow.
- Discarding a model because the fitted curve is "too steep" is only acceptable when there is scientific justification.
- Clearly articulate the criteria for determining that models are reasonable as well as providing transparent definitions for frequently used terms such as "too steep," "unstable," "problematic," and "credible".
- Assign weight to various models based on a modified combination of biological plausibility and statistical considerations; use somewhat different considerations for comparing AICs than those currently employed in the draft assessment.
- Use a different set of emphases in the priorities for the most reasonable models; detailed suggestions are provided by the SAB in this response.

2c: For analyses using a two-piece spline model, please comment on whether the method used to identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically appropriate.

The method used to identify the knots involves a sequential search over a range of plausible knots to identify the value at which the likelihood is maximized. This is scientifically appropriate and a practical solution that is transparently described.

The quote from EPA states "[The knot is preselected and is not considered a parameter in these analyses, consistent with the SAB's concept of parsimony (SAB, 2015)]." However, EPA also states on footnote a to Table D-27 "knots were obtained by doing a grid search by increments of 100 ppm x days and then interpolating where appropriate" and foot note b states "For models with very low knots, alternate knots were obtained from local maximum likelihoods because of the small number of cases informing the slope of the low-exposure spline for low knots (see Figure D-14)." EPA further states on page D-41 (emphasis added) "For the two-piece log-linear model, the single knot was chosen at 100 ppm-days based on a comparison of likelihoods assessed every 100 ppm-day from 100 to 15,000. The best likelihood was at 100 ppm-days. Figure D-15 below shows the likelihood versus the knots. Figure D-15 also suggests a local maximum likelihood near 1,600 ppm-days."

In summary, EPA's description of how the knots for the linear spline and log-linear spline models were found clearly indicate that the knots were not fixed parameters, but rather were optimized numerically and in this way were estimated from the data that were fit. That is, the knots used by EPA for the linear and log-linear spline models were determined using the NIOSH data, so that the knot maximized the likelihood of the spline model. The knots, therefore, were not fixed parameters independent of the NIOSH data, as would be the case in SAB discussion of an example. EPA contradicts itself when it states "[The knot is preselected and is not considered a parameter in these analyses, consistent with the SAB's concept of parsimony (SAB, 2015)].[14]" The latter EPA statement is simply false, because each knot value derived by EPA was in fact optimized (i.e., estimated) by EPA to best fit a corresponding model to a specific set of data. This fact has no relevance at all to the concept of parsimony in model selection, which refers to preference for selecting among different models the one(s) that has (have) the fewest total number (k) of estimated parameters. The parsimony concept is also expressed in the definition of the Akaike Information Criterion (AIC), which is proportional to the value of k, insofar as superior models are identified as those with smaller associated values of AIC. Likewise, a p-value for goodness of model fit is typically evaluated in relation to a corresponding value of the total number of degrees of freedom (DF) associated with that fit, and the latter number is always defined as the total number (n) of data points modeled minus the total number (k) of estimated model parameters, i.e., DF = n–k. An invalid reduction in k (e.g., by improperly considering a parameter "fixed" when in fact it was estimated to get a best fit for that model), therefore always improperly inflates the value of DF, which results in an erroneously high p-value for goodness-

of-fit that falsely magnifies the likelihood that deviations between data and a model fit to those data are due only to chance (i.e., due only to sampling error).

Misinterpretation of Degrees of Freedom Results in Miscalculated p-values, AIC and Incorrect Model Selection

The "log-linear spline model with knot at 1,600 ppm-days" has three parameters that each were estimated: slope below the knot, slope above the knot, and the knot itself. However, when EPA calculated a corresponding p-value associated with its reported chi-square test for improved fit relative to an associated null model, EPA used only two degrees of freedom for this calculation. This resulted in artificially and erroneously inflating the measure of improved fit used to compare the linear spline model to other models for which p-values were calculated using degrees of freedom that accurately reflected the total number of estimated parameters associated with other model fits being compared. Specifically, EPA did not include the degree of freedom associated with the separate procedure EPA applied to numerically and graphically maximize the log likelihood of each linear spline model for which an optimum knot value was also estimated. By failing to account for the degree of freedom associated with knot-estimation, the p-value EPA reported for each such linear spline model was miscalculated to yield a lower p-value (indicating an unrealistically improved fit) than would be produced had the correct number of degrees of freedom been used by EPA for each such calculation.

In using the approach EPA took in this regard, EPA may have misinterpreted comments of the EPA (2015) Science Advisory Board (SAB) review of the EPA (2014) draft IRIS document, which on pages 12–14 state that:

> the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered. Attention to this principle becomes even more important as the information in the analysis dataset becomes even more limited. Thus, models with very few estimated parameters should be favored in cases where there are only a few events in the dataset. To elaborate further, in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, **fixing the knot when estimating linear spline model fits from relative risk regressions is one such example**. … differences in AICs could be an artifact of how the calculation was done.

Importantly (as shown above), although the SAB indicated that fixing a knot value can be done as part of a practical approach to knot-value estimation, it also stated that "differences in AICs could be an artifact of how the calculation was done." The SAB unfortunately failed to emphasize (but must be assumed to agree with the fact) that **differences in p-values from chi-square tests of improved fit relative to the null model can also reflect non-meaningful**

artifacts if associated p-value calculations are not done correctly. Specifically, it is not meaningful to compare (as EPA did) a p-value from a Cox linear-regression model of Log(RR) on ppm-days of exposure (defined to be associated with one degrees of freedom for each of the estimated slope of the line) to a p-value from EPA's linear spline model fit (assumed to be associated with only two degrees of freedom corresponding to its two estimated slopes) conditional on a knot value that EPA estimated by minimizing log likelihood in relation to the knot value. EPA incorrectly assumed its optimized knot-value estimate is not associated with one additional degree of freedom. Thus, EPA erroneously deflated the total degrees of freedom associated with their three-parameter linear model by evaluating it as if it had only two degrees of freedom (parameters) associated with it. Consequently, EPA miscalculated the p-value for its spline model resulting in an erroneously low p-values of ~0.07 (see Table 2), when (as explained in more detail in the next section) the correctly calculated p-value is ~2-fold greater (i.e., 0.14 to 0.15) and do not differ meaningfully from p-values associated with the more parsimonious linear Cox regression model (see corrected Table 4-6 discussed in the next section).

Table 2. SAS results given for this model in Table D-33 in Appendix D of EO IRIS 2016

Table D-33. Results of two-piece log-linear spline model for lymphoid cancer mortality, men and women combined, knot at 1,600 ppm-days

Model fit statistics						
Criterion	**Without covariates**	**With covariates**				
-2 LOG L	463.912	**458.640**				
AIC	463.912	**462.640**				
SBC	463.912	466.581				
Testing global null hypothesis: BETA = 0						
Criterion	**Without covariates**	**With covariates**				
Likelihood ratio	5.2722	**2**	**0.0716**			
Score	5.2666	2	0.0718			
Wald	5.1436	2	0.0764			
Analysis of maximum likelihood estimates						
Parameter	**DF**	**Parameter estimate**	**Standard error**	**$\chi 2$**	**Pr > ChiSq**	**Hazard ratio**
LIN_0	1	0.0004893	0.0002554	3.6713	0.0554	1.000
LIN_1	1	0.0004864	0.0002563	3.6014	0.0577	1.000

Miscalculated p-values: Example using the log-linear spline model with knot at 1,600 ppm-days"

The likelihood ratio test is used to test whether a fitted model significantly improves the fit of the data by estimating parameters instead of just assuming a baseline (null) model for the data. The likelihood ratio test is evaluated by comparing the likelihood of the model with the estimated parameters and the likelihood of the null model. If the likelihood of the model with the estimated parameters is equal to the likelihood of the null model, then the natural logarithm of the ratio of

these likelihoods multiplied by two follow a Chi-Square distribution with as many degrees of freedom as the number of parameters estimated for the fitted model. Thus, if the fit of the baseline (null) model and the model with estimated parameters are not different,

$$Chi - Square(k) = \chi_k^2 = -2 \ln \left(\frac{likelihood\ for\ null\ model}{likelihood\ for\ fitted\ model} \right)$$

This can also be written as follows,

$$\chi_k^2 = -2LogL(null\ model) - 2LogL(fitted\ model)$$

Here k is the number of degrees of freedom (k is the number of parameters that were estimated in excess of the parameters estimated for the null model).

For the model in Table 2 (Table D-33 in EO IRIS 2016) the χ_k^2 value was equal to 5.2722 and k was set to 2. This resulted in a p-value of 0.0716. That is, the fitted model was assumed to have two parameters; namely, the slope below the knot and the slope above the knot. The results in Table 2 are from a SAS output for the model specified. The model specified included a knot. This knot was determined so that the likelihood of the spline model was maximized. That is, the knot is another parameter that was searched for outside SAS. Because the estimation of the "knot" was done outside SAS, the SAS program did not count the knot as a parameter and, consequently, the Chi-Square test SAS reported does not reflect the fact that the knot was also estimated. The correct Chi-Square that accounts for the fact that the knot was estimated outside SAS should then be 5.2722, but k (the degrees of freedom) should be 3. This corrected calculation would result in a p-value of 0.1529. That is, the corrected p-value indicates that the likelihood of the "log-linear spline model with knot at 1,600 ppm × days" is not different from the likelihood of the null model. In plain words, there is not enough evidence indicating that the fitted log-linear spline model explains the variability in the data any better than the null model.

Miscalculated AICs: Example using the log-linear spline model with knot at 1,600 ppm-days

The Akaike Information Criterion (AIC) is equal to $2k$ - $2LogL$ where k is the number of parameters estimated for the model and LogL is the logarithm of the likelihood. Here, Table 2 (Table D-33 in EO IRIS 2016) lists the -2LogL as 458.640 and the AIC as 462.640. That is;

$$462.640 = 2k + 458.640$$

The AIC and –2LogL implies that k equals 2. That is, the spline model was assumed to have estimated two parameters; namely, the slope below the knot and the slope above the knot. The results in the Table 2 consist of SAS output for the spline model specified. The model specified included a knot. This knot was pre-assigned (i.e., previously estimated using a separate optimization procedure outside the SAS run), so the likelihood of the model was maximized only

conditional on the estimated knot-value used for that calculation. Consequently, the knot must be treated as an additional parameter that was estimated outside SAS. Because the estimation of the "knot" was done outside SAS, the SAS run performed by EPA did not count the knot as a model parameter and, consequently, the resulting AIC value it obtained does not reflect that the knot was in fact estimated. EPA could have requested SAS to account properly for the extra degree of freedom properly associated with its estimated knot value, but EPA evidently elected not to make this request of SAS.

The correct AIC, which accounts for the fact that the knot was estimated outside SAS, should instead be

$$\text{AIC} = 464.640 = 2\times 3 + 458.640$$

These differences are summarized in corrected Table 3 below.

Model selection with correct AIC and p-values

EPA selects the "linear spline model with knot at 1,600 ppm × days" for lymphoid for the following reasons:

a) Adequate statistical fit. EPA's uses the erroneous p-value of 0.07 (Table 1) to select the model arguing that it is close to 0.05. However, the corrected p-value is 0.14 (Table 3) once the fact that the knot was also estimated is accounted for by adding one more degree of freedom to the chi-square distribution. The corrected p-value is now in the range of the p-values for the log-linear and linear models; in fact, it is larger than the p-value (0.13) for the linear model.

b) Adequate visual fit. EPA's visual fit is dismissed in the footnote of Figure 4-3 of the EO IRIS 2016 report. The footnote reads "(Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis. They are, however, comparable in terms of general shape.)" In addition to the visual-fit caveat listed by EPA in the IRIS report, they failed to indicate that the models are **not** fit to the five nonparametric rate ratios shown in the figure, but rather to the individual cases that includes nine cases of lag-15 EO unexposed workers and 44 cases with lag-15 EO cumulative exposure. That is, the graph shown in Figure 4-3 of the EO IRIS 2016 report does not show all the variability in the full data and visual comparisons can be misleading. Furthermore, the categorical rate ratios are not "the data", but rather, non-parametric estimate of the rate ratios.

c) Including local fit (visual) **to low-exposure range; linear model.** When the models are plotted against the non-parametric rate ratios of the 44 exposed cases, all models seem to fit the

non-parametric models about the same; which is consistent with the calculated p-values and AIC values.

d) AIC within two units of lowest AIC of models considered. EPA's uses the erroneous AIC value of 462.1 to select the model arguing that it is within two units from the lowest AIC (460.2 for the "linear model with log cumulative exposure"). However, the corrected AIC is 464.5 once the fact that the knot was also estimated is accounted for by adding one more parameter in the calculation of the AIC. The corrected AIC for the "linear spline model with knot at 1,600 ppm-days" is now larger than the AIC values for the linear model (463.6) and for the log-linear model (464.4).

Once the errors indicated above concerning calculating p-values, calculating AIC values, and associated adjustments for different calculations of likelihood values are all corrected, EPA's best model for lymphoid should be reconsidered. Using the criteria EPA EO IRIS uses to select a model, the best models for the lymphoid data are the "linear model" followed by the "log-linear model."

Table 3. The following table has been extracted from EO IRIS 2016 Table 4-6 and the p-values and AIC values have been corrected to reflect the degree of freedom for the knot in the spline models and to reflect the likelihood difference between SAS procedures used for linear and log-linear models

Table 4–6. Models considered for modeling the exposure-response data for lymphoid cancer mortality in both sexes in the National Institute for Occupational Safety and Health cohort for the derivation of unit risk estimates

Model[a]	*p-value*[b]	AIC[c]	Comments
Two-piece spline models			
Linear spline model with knot at 1,600 ppm × days	0.14	464.5	**SELECTED.** Adequate statistical and visual fit, including local fit to low-exposure range; linear model; AIC within two units of lowest AIC of models considered.
Linear spline model with knot at 100 ppm × days	0.11	463.8	Good overall statistical fit and lowest AIC of two-piece spline models, but poor local fit to the low-exposure region, with no cases below the knot.
Log-linear spline model with knot at 1,600 ppm × days	0.15	464.6	Linear model preferred to log-linear (see text above).
Log-linear spline model with knot at 100 ppm × days	0.11	463.8	Good overall statistical fit and tied for lowest AIC_c of two-piece spline models, but poor local fit to the low-exposure region, with no cases below the knot.
Linear (ERR) models (RR = 1 + β × exposure)			
Linear model	0.13	463.6	Not statistically significant overall fit and poor visual fit.
Linear model with log cumulative exposure	0.02	460.6	Good overall statistical fit, but poor local fit to the low-exposure region.

Appendix 1

Model[a]	*p-value*[b]	AIC[c]	Comments
Linear model with square-root transformation of cumulative exposure	0.053	462.2	Borderline statistical fit, but poor local fit to the low-exposure region.
Log-linear (Cox regression) models (RR = $e^{\beta \times \text{exposure}}$)			
Log-linear model (standard Cox regression model)	0.22	464.4	Not statistically significant overall fit and poor visual fit.
Log-linear model with log cumulative exposure	0.02	460.4	Good overall statistical fit; lowest AIC[c] of models considered; low-exposure slope becomes increasingly steep as exposures decrease, and large unit risk estimates can result; preference given to the two-piece spline models because they have a better ability to provide a good local fit to the low-exposure range.
Log-linear model with square-root transformation of cumulative exposure	0.08	462.8	Not statistically significant overall fit and poor visual fit.

[a]All with cumulative exposure as the exposure variable, except where noted, and with a 15-yr lag.

[b]*p*-values from likelihood ratio test, except for linear regression of categorical results, where Wald *p*-values are reported. $p < 0.05$ considered "good" statistical fit; $0.05 < p < 0.10$ considered "adequate" statistical fit if significant exposure-response relationships have already been established with similar models.

[c]AICs for linear models are directly comparable and AICs for log-linear models are directly comparable. However, for the lymphoid cancer data, SAS proc NLP (where NLP = nonlinear programming) consistently yielded −2LLs and AICs about 0.4 units lower than proc PHREG for the same models, including the null model, presumably for computational processing reasons, and proc NLP was used for the linear RR models. Thus, AICs for linear models are equivalent to AICs about 0.4 units higher for log-linear models. No AIC was calculated for the linear regression of categorical results.

Note: In order to make the AICs comparable for different models, the AIC's for the linear models have been increased by 0.4 to reflect the discrepancy in the -2LogL values reported by the SAS proc NLP and by SAS PHREG (as indicated in green in this table).

Figures 1 to 4 are versions of EPA's Figure 4-3. A model (TrueLogL – dotted light blue line in the graphs) was added to relieve the caveat posed by EPA in the footnote to Figure 4-3 about the visual comparability of fitted models. The TrueLogl model is an approximation to the correct visual representation of the log-linear (standard Proportional Hazards Model fit to the NIOSH full data set) after adjusting for the difference in baseline risks between the rate ratios and the loglinear model. In Figures 1 to 4, all the individual RR (categorical) in the light blue box of the figure are summarized by the red dot in the light blue box (EPA's 5 RRs for the last quartile). Similarly, all the individual RR (categorical) in the light yellow box of the figure are summarized by the red dot in the light yellow box (EPA's 5 RRs for the third quartile). In the same way, all the individual RR (categorical) in the light green box of the figure are summarized by the red dot in the light green box (EPA's 5 RRs for the second quartile). Finally, all the individual RR (categorical) in the clear box, next to the vertical axis of the figure, are summarized by the red dot in the clear box (EPA's 5 RRs for the first quartile).

Appendix 1

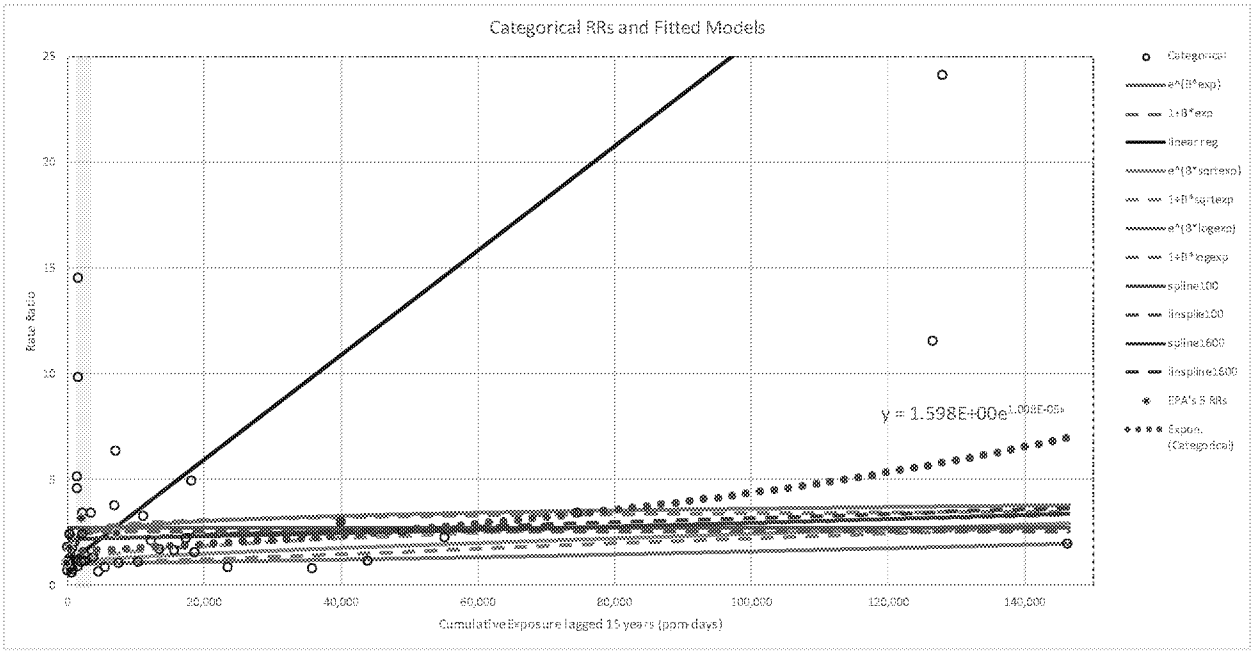
Figure 1 shows all EPA models plotted versus the individual nonparametric rate ratios (categorical) and grouped rate ratios (EPA's 5 RRs). The range of cumulative exposures when the rate ratios for all cases are plotted is much bigger than the range of cumulative exposures when the rate ratios are averaged over several cases (EPA's 5 RRs). The variability of the rate ratios for the individual cases (categorical) is much larger than the variability of the rate ratios averaged over several cases (EPA's 5 RRs). Except for the unacceptable linear model fit to four rate ratios (linear reg), all models fit approximately the same in Figure 1. The model Expon. (Categorical) is a plot of the approximate log-linear model (e^(B*exp)) adjusted by dividing the model for the hazard rate by the baseline hazard rate of the nonparametric estimates.

Figure 2 shows an expansion of the low-left corner of Figure 1. These are all EPA models plotted versus the nonparametric rate ratios with values between 0 and 3.5 and cumulative exposures between 0 and 40,000 ppm-days. This graph resembles Figure 4-3 of the EO IRIS 2016 report with the exception that rate ratios based on individual cases (categorical) that are in the range of the graph are plotted in addition to the aggregated four points used by EPA (EPA's 5 RRs).

Figure 3 is the same as Figure 1 except that the vertical scale is shown using a logarithmic scale of the rate ratios to visualize the linear difference between the fitted models and the rate ratios.

Figure 4 is the same as Figure 2 except that the vertical scale is shown using a logarithmic scale of the rate ratios to visualize the linear difference between the fitted models and the rate ratios.

Figure 1. EPA models plotted against all lymphoid rate ratios in the NIOSH data



Appendix 1

Figure 2. EPA models plotted against all lymphoid rate ratios in the NIOSH data in the low exposure concentration range and with the rate ratio truncated to the same range of EPA's Figure 4-3.

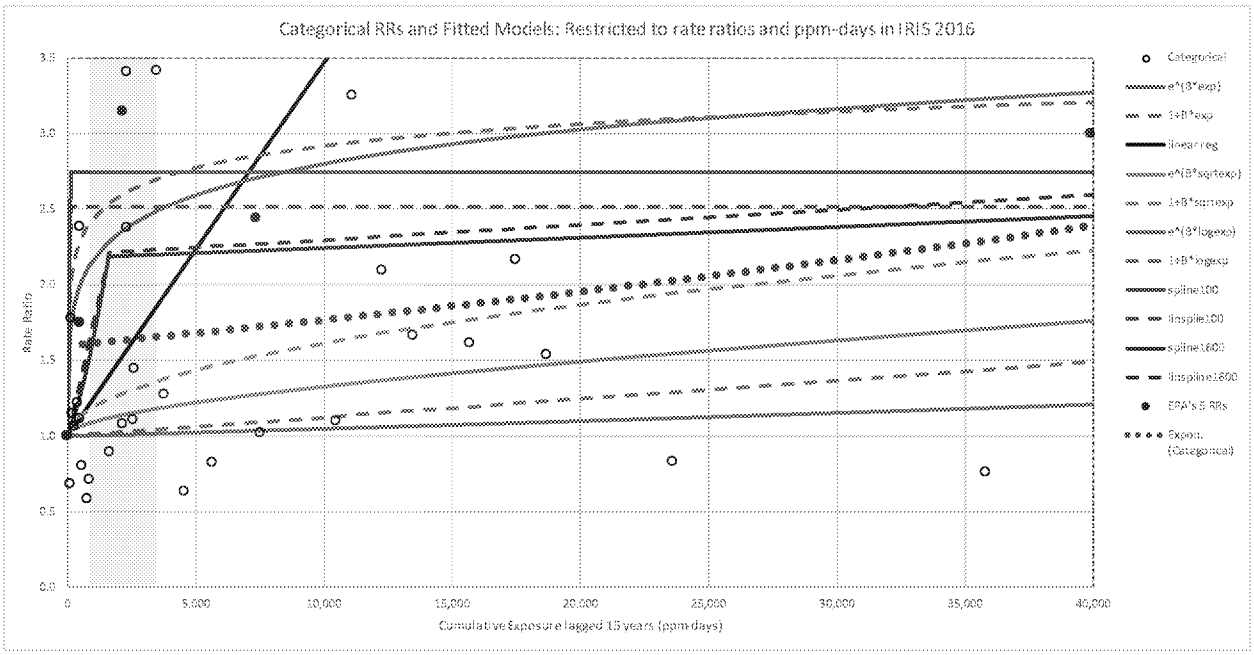
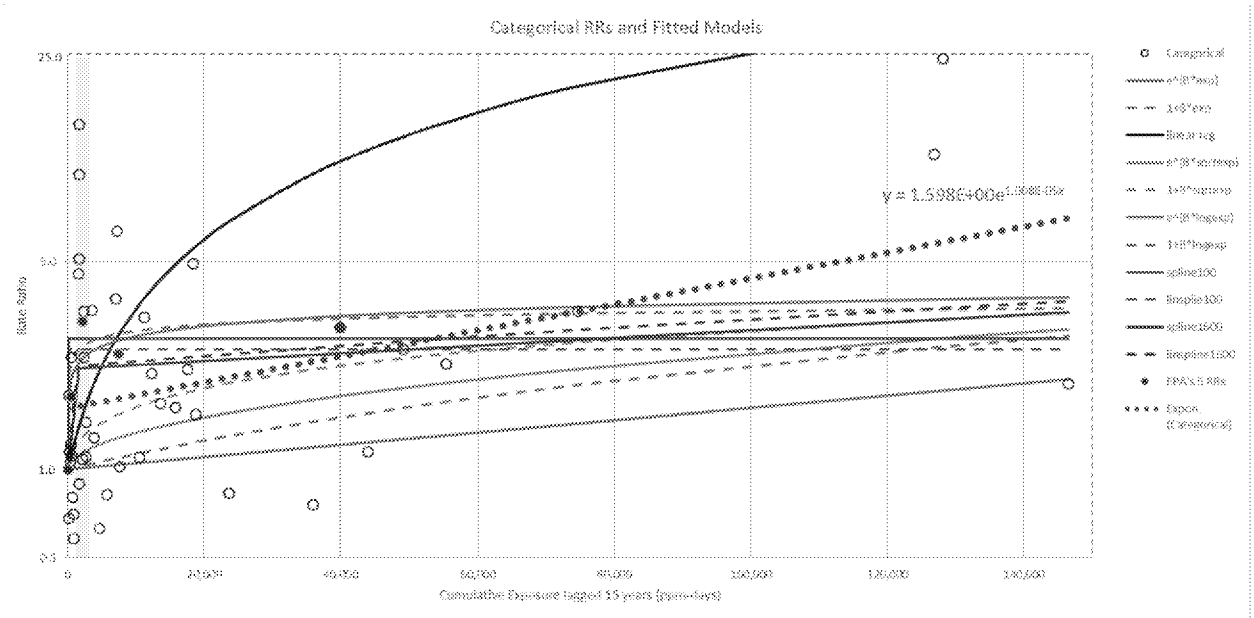
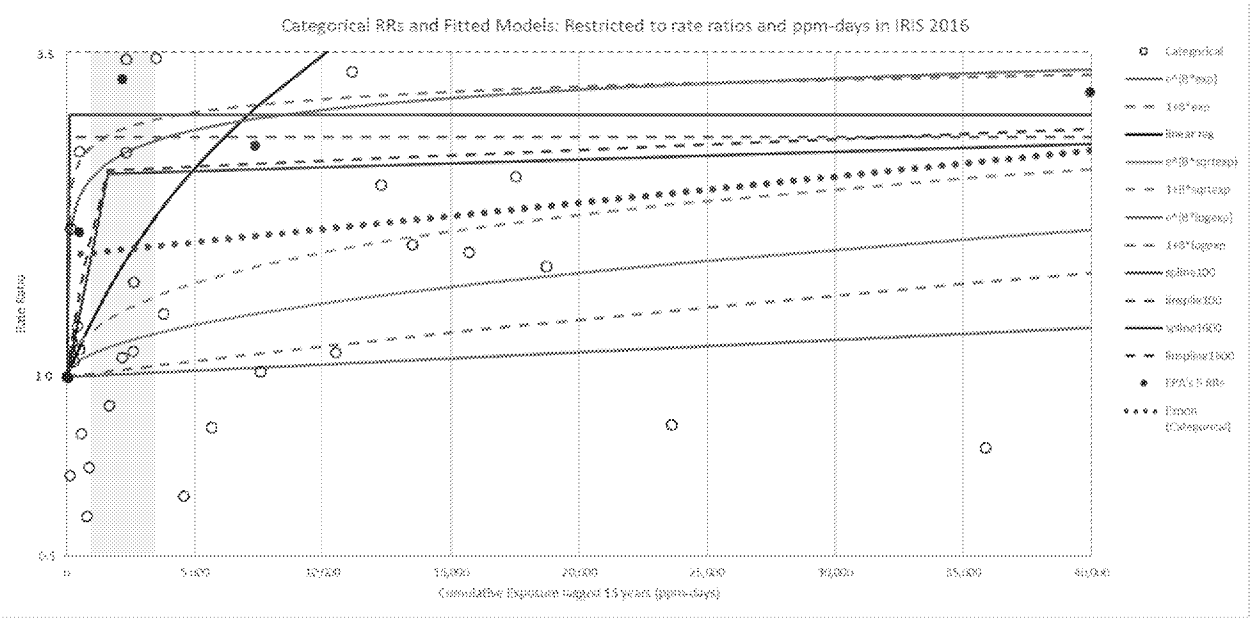


Figure 3. EPA models plotted against the logarithm of all lymphoid rate ratios in the NIOSH data



Appendix 1

Figure 4. EPA models plotted against the logarithm all lymphoid rate ratios in the NIOSH data in the low exposure concentration range and with the rate ratio truncated to the same range of EPA's Figure 4-3.



Appendix 2

Brief Summary of Epidemiological Data for EO

M. Jane Teta, Dr.P.H., M.P.H.
Exponent Health Sciences

The relevant epidemiology, despite the large number of studies published over a forty-year period, are not supportive of a determination that EO is a human carcinogen. While interest has centered on leukemia, other blood related malignancies, and recently breast cancer: (1) there are numerous inconsistencies across the studies, (2) elevated risks above background are found in isolated studies and the effect size is of small magnitude, and (3) there is an absence of a clear exposure-response relation for any specific cancer type.

Examination of the specific cancer subtypes (leukemia, non-Hodgkin's lymphoma [NHL], Hodgkin's disease [HD], multiple myeloma [MM] and lymphohematopoietic cancers [LH] overall) illustrates the absence of clear evidence of carcinogenicity and no clear choice for a target organ should a dose-response be attempted. Table 1 summarizes the individual and overall findings from the EO studies for leukemia. Taking the ratio of the total observed cases and the total expected number of cases yields a summary risk estimate. The total number of deaths due to leukemia is 64 with 56.86 expected for an SMR /SIR of 1.13 (95% CI: 0.87-1.44). It is noteworthy that Hogstedt's increase was mainly attributable to myeloid leukemias, while Steenland focused on lymphocytic leukemia in the lymphoid category. As shown by Shore and Teta in their meta-analyses, Hogstedt is an outlier that is statistically different in findings from the other studies, i.e., a cause of heterogeneity. Furthermore, it is incorrect to include a cluster which gave rise to the hypothesis in a summary risk estimate. Excluding Hogstedt, yields 57 observed leukemias and 56.06 expected for an SMR/SIR of 1.02 (95% CI: 0.77, 1.32). Clearly Hogstedt's hypothesis of EO as a cause of leukemia has not been confirmed.

Appendix 2

Table 1. Leukemia in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	7	0.80	9.21* (3.70, 19.0)
Lymphocyctic	2	---	---
Myeloid	3	---	---
NOS	2	---	---
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	5	3.58	1.40 (0.45, 3.26)
Thiess 1981/Kiesselbach 1990	2	2.35	0.85 (0.10, 3.07)
Morgan 1981/Divine 1990	0	0.60	0.00 (0.00, 6.57)
Greenberg 1990/Teta 1993/ Swaen 2009	11	11.8	0.93 (0.47, 1.67)
Steenland 1991/Stayner 1993/ Steenland 2004	29	29.3	0.99 (0.71, 1.36)
Bisanti 1993	2	0.30	6.50 (0.79, 23.5)
Gardner 1989/Coggon 2004	5	4.60	1.08 (0.35, 2.51)
Olsen 1997	2	3.00	0.67 (0.08, 2.40)
Norman 1995	1	0.54	1.85 (0.05, 10.3)
Summary	64	56.9	1.13 (0.87, 1.44)
Summary (-Hogstedt)	57	56.1	1.02 (0.77, 1.32)

For HD there were 17 observed compared to 10.84 expected (1.57; 95% CI: 0.91-2.51) (Table 2). The Swaen case-control study was included and an expected number was derived to combine these results with those of the cohort studies. (The proportion of controls exposed, 5%, was applied to the case group of 10 cases yielding an expected exposed of 0.5). Relying only on the two strongest studies (Swaen 2009 and Steenland 2004) yields for HD, 6 vs. 6.54 (0.92; 95% CI: 0.34, 2.0). The Swaen 2009 UCC cohort had no deaths due to HD.

Appendix 2

Table 2. Hodgkin Disease in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	0	---	---
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	1	1.31	0.76 (0.02, 4.25)
Thiess 1981/Kiesselbach 1990	---	---	---
Morgan 1981/Divine 1990	3	0.40	8.34* (1.68, 24.4)
Greenberg 1990/Teta 1993/ Swaen 2009	0	1.70	0.00* (0.00, 0.22)
Steenland 1991/Stayner 1993/ Steenland 2004	6	4.84	1.24 (0.53, 2.43)
Bisanti 1993	---	---	---
Gardner 1989/Coggon 2004	2	1.05	1.91 (0.23, 6.89)
Olsen 1997	2	0.70	2.86 (0.35, 10.3)
Norman 1995	0	0.34	0.00 (0.00, 10.9)
Swaen 1996	3	0.50	8.50* (1.40, 39.9)
Summary	17	10.8	1.57 (0.91, 2.51)

Two studies provided no data for MM (Kiesselbach 1990 and Bisanti 1993) and four others failed to provide expected values (Hogstedt 1988, Divine 1990, Olsen 1997, and Swaen 2009) (Table 3). Upon contacting Dow, we were able to obtain the expected number of 5.1 for MM. Based on the studies with complete information, there are 22 observed and 24.0 expected for a summary estimate of 0.92 (Table 3). This result is heavily weighted by the largest study, Steenland et al. 2004, who reported 13 cases vs. 14.13 expected (SMR= 0.92). This summary risk estimate does not indicate an association with MM.

Appendix 2

Table 3. Multiple Myeloma in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	0	---	---
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	2	2.08	0.96 (0.12, 3.47)
Thiess 1981/Kiesselbach 1990	---	---	---
Morgan 1981/Divine 1990	0	---	---
Greenberg 1990/Teta 1993/ Swaen 2009	3	5.10	0.59 (0.12, 1.72)
Steenland 1991/Stayner 1993/ Steenland 2004	13	14.1	0.92 (0.49, 1.57)
Bisanti 1993	---	---	---
Gardner 1989/Coggon 2004	3	2.50	1.20 (0.25, 3.49)
Olsen 1997	1	NR	NR
Norman 1995	1	0.23	4.34 (0.11, 24.2)
Summary	22	24.0	0.92 (0.57, 1.39)

Using the same method of pooling the observed and expected values of NHL across the different studies results in a meta-SMR/SIR estimate of 1.12 based on 62 observed and 55.4 expected, a small, non-statistically significant increase (Table 4).

Table 4. Non-Hodgkins Lymphoma in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	2	---	---
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	9	6.25	1.44 (0.66, 2.73)
Thiess 1981/Kiesselbach 1990	---	---	---
Morgan 1981/Divine 1990	0	0.90	0.00 (0.00, 4.04)
Greenberg 1990/Teta 1993/ Swaen 2009	12	11.5	1.05 (0.54, 1.83)
Steenland 1991/Stayner 1993/ Steenland 2004	31	31.0	1.00 (0.72, 1.35)
Bisanti 1993	3	0.20	16.9* (3.49, 49.5)
Gardner 1989/Coggon 2004	7	4.80	1.46 (0.59, 3.02)
Olsen 1997	5	NR	NR
Norman 1995	0	0.76	0.00 (0.00, 4.85)
Summary	62	55.4	1.12 (0.86, 1.43)

Examination across the ten studies of all LH cancers yields a non-statistically significant increase based on 175 observed vs. 156.97 expected (Meta-SMR/SIR = 1.11; 95% CI: 0.96, 1.29) (Table 5). Exclusion of Hogstedt would result in a weak excess (1.07) and narrow confidence interval (95% CI: 0.91, 1.25).

Appendix 2

Table 5. All Lymphopoietic and Hematopoietic Cancers in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	9	2.00	4.59* (2.10, 8.70)
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	18	14.4	1.25 (0.74, 1.98)
Thiess 1981/Kiesselbach 1990	5	4.99	1.00 (0.32, 2.34)
Morgan 1981/Divine 1990	3	3.00	1.01 (0.20, 2.96)
Greenberg 1990/Teta 1993/ Swaen 2009	27	30.4	0.89 (0.59, 1.29)
Steenland 1991/Stayner 1993/ Steenland 2004	79	79.0	1.00 (0.79, 1.24)
Bisanti 1993	5	0.70	7.00* (2.27, 16.4)
Gardner 1989/Coggon 2004	17	12.9	1.30 (0.77, 2.10)
Olsen 1997	10	7.70	1.29 (0.62, 2.38)
Norman 1995	2	1.88	1.06 (0.13, 3.84)
Summary	175	157.0	1.11 (0.96, 1.29)
Summary (-Hogstedt)	166	155.0	1.07 (0.91, 1.25)

As discussed above, Steenland et al. (2004) grouped three LHC cancers into the "lymphoid" category and reported some positive findings for men only. This category included lymphocytic leukemias only. The original cluster reported by Hogstedt in 1979 consisted of myeloid leukemias (Table 2). The results from the only other study to examine the lymphoid category as defined by NIOSH (UCC cohort) are inconsistent with the NIOSH results (Swaen 2009). From an internal analysis using Cox proportional hazard model, no evidence of an exposure–related response was observed by Swaen et al. using the UCC EO cohort. In fact, the females in the NIOSH study are also inconsistent with the male findings for lymphohematopoietic and "lymphoid" tumors (Steenland 2004).

Steenland et al. also examined both incidence and mortality from breast cancer for the sterilizer cohort (Steenland 2003, 2004). Among the overall results for this disease endpoint among other studies, only Norman et al. (1995) reported an increase (Table 6). Hogstedt enumerated all the cancers from his numerous cohorts and updates. No breast cancer cases were identified. Similarly, there was no excess among the hospital workers studies by Coggon et al. (2004), even among those with "continual" exposure (5 observed, 7.2 expected). The data related to breast cancer derived predominately from the NIOSH studies of sterilant workers with 102 deaths and 103 expected for an SMR of 0.99 (95% CI: 0.81-1.20) (Steenland 2004) and 319 incident cases with 367 expected for a statistically significant deficit of 0.87 (95% CI: 0.77-0.97) (Steenland 2003) due to underascertainment of cases. When examined in various exposure subgroup analyses, however, NIOSH concluded there was some evidence of an increase for breast cancer.

Appendix 2

Table 6. Ethylene Oxide Epidemiology Studies of Female Breast Cancer

Study	Observed	Expected	Obs./Exp. (95% CI)
Coggon et al. 2004	11	13.1	0.84 (0.42, 1.51)
Steenland et al. 2004	102	103.0	0.99 (0.81, 1.20)
Steenland et al. 2003	319	367.0	0.87* (0.77, 0.97)
Mikoczy et al. 2011	41	50.9	0.81 (0.58, 1.09)
Norman et al. 1995	12	7.0	1.72 (0.93, 2.93)
Hogstedt et al. 1986	0	---	---
Summary (incident cases only)	372	424.9	0.88* (0.79, 0.97)
Summary (mortality cases only)	113	116.1	0.97 (0.80, 1.17)

EPA recognizes that magnitudes of increased risks for breast cancer were not large and implies that the evidence is weaker than that for lymphoid tumors. Despite these issues, EPA proceeds to introduce breast cancer as a target organ in the IRIS Assessment and inappropriately develops a risk value. Uncertainties described by Steenland et al. (2003) related to the breast cancer incidence study are dismissed as unimportant by EPA. EPA agrees with Steenland that the breast cancer incidence findings are not conclusive, due to inconsistencies in the exposure-response and an incomplete cancer ascertainment. Using these data, the slopes of EPA's attempted exposure-response analyses were non-statistically significant or biologically uninterpretable, leading them to employ novel approaches for quantitative risk assessment. The modeling challenges could be anticipated given Steenland's statement of uncertainty with respect to breast cancer, "The dip in the spline curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure."

The Agency downplays the potential for selection bias based on the consistency in the incidence study between results from full cohort and those from the subgroup interviewed (68% of study subjects). Selection bias (referred to by Steenland as "possible biases due to patterns of non-response") remains a concern, however, with duration reported as a stronger risk factor than cumulative exposure in both analyses. Those who work longer stay in the area longer and are more likely to get picked up in the state tumor registries and be found for interview, therefore with the potential to impact the results of both analyses. Shorter duration workers with lower exposures are more likely to leave the area and not be captured in the overall analyses and less likely to be interviewed. Their diagnoses get missed, creating a possible biased positive exposure-response. Steenland recognized this limitation and admitted he was unable to fully address it and listed it as one of his uncertainties:

> A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies

under study, and hence greater cumulative exposure. Unfortunately, we did not have residential history, limiting our ability to explore this possibility.

The more recent study by Mikoczy et al. (2011) has been cited as supportive of an association with breast cancer, in spite of an overall deficit (SIR=0.81; 95% CI: 0.58-1.09) based on 41 cases observed. With 15-year latency it is 0.86, also suggesting no increase. Similar to NIOSH, however, the two higher cumulative exposure groups (of three total group) had statistically significant elevated rates of breast cancer (2.76; 95% CI: 1.20-6.33 and 3.55; 95% CI: 1.58-7.93) in an *internal* Poisson analysis, due, however, to a substantial and statistically significant deficit of breast cancer in the low dose reference group (SIR=0.52; 95% CI: 0.25-0.96). There are clearly advantages to comparing workers to workers in epidemiology studies to overcome possible biases in external comparisons to the general population. However, there may also be disadvantages to using an internal comparison group that are not recognized. One danger is selecting a referent group that has an unusual excess or deficit of the disease of interest as illustrated in this study. This illustrates the problem that can arise from internal comparisons and should not always to be preferred despite what EPA contends.

In addition to LH cancers, EPA uses breast cancer as a target endpoint. We conclude that the choice of breast cancer as a target organ for EO dose-response assessment is not justified for several reasons: (1) EPA agrees that the evidence for breast cancer is even weaker than the evidence for the lymphoid category, (2) the NIOSH findings suffer from potential selection biases, show a non-monotonic increase in risk with increasing exposure, and neither mortality nor incidence rates overall exceed background rates in the general population, and (3) the breast cancer findings from the other epidemiology studies are equivocal.

There is no obvious target organ for an EO exposure-response assessment for a quantitative risk assessment. Given the weak epidemiology evidence for carcinogenicity, the lack of consistency or a clear exposure-response, the selection of a specific target organ is problematic. Using cumulative exposure as the exposure metric and the standard proportional hazard modeling, none of the slopes for the endpoints of interest are statistically significant (Valdez-Flores, Sielken, and Teta 2010). Despite the absence of a clear exposure-response for any one of the combinations, the authors proceeded to use EPA's standard procedure for unit risk estimation and estimation of exposure associated with a one-in-a-million risk. This approach was adopted by Scientific Committee on Occupational Exposure Limits (SCOEL) for the European Union in 2012 for occupational standard setting.

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Message

From: McClintic, Howard [McClintH@ctc.com]
Sent: 2/15/2018 8:10:50 PM
To: Wehrum, Bill [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33d96ae800cf43a3911d94a7130b6c41-Wehrum, Wil]
Subject: Saving Hundreds of Millions of Taxpayers' Dollars Remediating Superfund Sites -- Get Rid of the LNT!
Attachments: FINAL LNT Presentation of Howard McClintic.pptx; Intro Email to EPA-LNT Project

Importance: High

CTC Foundation

Ensuring the Future Through Innovation, Science and Technology

1235 S. Clark St. Ste. 715
Arlington, VA 22202
(703) 310-5688 (703) 310-5655 FAX
(202) 689-4586 Mobile
E-Mail: McClintH@ctc.com
Tax-Exempt Number: 25-1811888

Good Day Mr. Wehrum:

Our mutual friend, Mark Bierbower, and I have discussed this Project countless times! My colleague, Dr. Robert (Bob) Golden, and I would like to schedule some time soon to have a Conference Call with you. We want you to clearly understand our Goals and Objectives as well as the importance and purpose of our soon to be completed peer-reviewed Science Committee Report.

Toward this end, I am attaching my PowerPoint Presentation. Bob and I each realize that slides 7 through 11 as being the most important because they visually depict the distortive effects of the LNT sharply contrasted with (and compared to) science-based data points. As you are aware, even now and through time, the former EPA Administrator, Gina McCarthy, consistently and emphatically repeats in interviews as well as in testimony over four years ago (on November 14, 2013), before the US House of Representatives Committee on Science, Space and Technology, she testified:

> "...Let me begin by stating that science is and has always been the backbone of the EPA's decision-making. The Agency's ability to pursue its mission to protect human health and the environment depends upon the integrity of the science upon which it relies. I firmly believe that environmental policies, decisions, guidance, and regulations that impact the lives of all Americans must be grounded, at a most fundamental level, in sound, high quality, transparent, science..."

(https://science.house.gov/sites/republicans.science.house.gov/files/documents/HHRG-113-SY-20131114-SD001%20.pdf as well as http://www.c-span.org/video/?327016-1/epa-administrator-gina-mccarthy-testimony-proposed-regulations

As you know, the Goal of this project is to determine, through a rigorous analyses of both the radiation and chemical data, the comparative validity of the science. The ***CTC Foundation's*** Science Committee that will compare and contrast the scientific evidence for the LNT and threshold models for radiation- and chemical-induced cancer and non-cancer effects in humans. This Committee was empaneled in October, 2016 and is comprised of recognized experts, from diverse disciplines and backgrounds. Their purpose is to develop a comprehensive peer-reviewed publication. Bob Golden and Dr. Edward Calabrese (https://www.umass.edu/sphhs/person/faculty/edward-j-calabrese) are Co-Chairs of the Science Committee.

We look forward to our Conference Call as soon as possible. We are very grateful for your time, attention and assistance – Thank You.

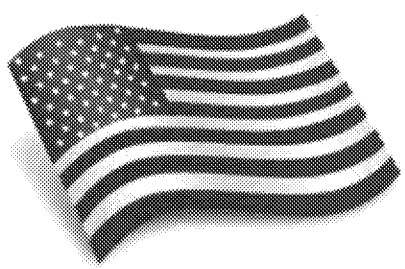
Most sincerely yours,

Howard

Howard G. McClintic

Executive Director

202 689 4586



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Message

From: McClintic, Howard [McClintH@ctc.com]
Sent: 2/2/2018 4:02:58 PM
To: McClintic, Howard [McClintH@ctc.com]
Subject: Intro Email to EPA-LNT Project
Attachments: FINAL one page LNT project summary 1-23-17.docx

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1235 S. Clark St. Ste. 715
Arlington, VA 22202
(703) 310-5688 (703) 310-5655 FAX
(202) 689-4586 Mobile
E-Mail: McClintH@ctc.com
http://www.ctcfoundation.org
Tax-Exempt Number: 25-1811888

Good Day,

My colleague, Dr. Robert (Bob) Golden and I are pleased to bring the important work of the ***CTC Foundation's*** Science Committee to your attention.

I am attaching a one page write-up of our Project that should provide the background that would be useful for a Conference Call that we would like to schedule with you at your convenience. Also, Bob put together this information summarizing the Science Committee's author, chapter title and status, which makes plain our progress.

Chapters	**Author**	**Status**
Prolog	Golden	Drafted
Introduction	Bus	In progress
History of LNT	Calabrese	Drafted
• LNT vs. threshold models: an evolutionary perspective	Costantini	Drafted
Why LNT needs to be abandoned of low-dose radiation risk assessment	Scott	Drafted
The impact of dose-rate on LNT hypothesis for radiation risk assessment	Brooks	Drafted
Thresholds for mutagenic carcinogens	Williams & Kobets	Drafted
Mechanistic aspects of chemical carcinogens demonstrating thresholds	H Clewell & R Clewell	In progress

Real world risks of chemical carcinogens assuming LNT is correct	Bus & Golden	To be drafted
Epidemiological analysis of low dose/dose rate radiation data	Ricci	Drafted
Economic implication of LNT vs. threshold models for benefit-cost analyses	Williams & Shamoun	To be drafted
Discussion & conclusions	All	To be drafted

Bob and I anticipate that you'll ask questions about this update and other matters during our conference call. Please suggest some dates and times for our Conference Call. We are grateful for your interest.

Many thanks, most sincerely yours,

Howard

Howard G. McClintic
Executive Director
202 689 4586

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 7/9/2018 11:51:28 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: new paper
Attachments: Environ. Res. Additive to Background.pdf

Clint

See the attached new paper....it represents a novel and very serious challenge to LNT.....totally overlooked before....
Please share widely with your colleagues....
If you would ever want me to give a seminar to epa headquarters on the limitations of LNT let me know.

Ed

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 5/7/2018 7:48:57 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: RE: LNT obit

Clint:

I have now drafted my comments for the recent EPA initiative.

Ed

From: Woods, Clint <woods.clint@epa.gov>
Sent: Monday, May 7, 2018 3:17 PM
To: Edward Calabrese <edwardc@schoolph.umass.edu>
Subject: RE: LNT obit

Dr. Calabrese,

Sorry for the delay – Thanks so much for passing this along.

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

From: Edward Calabrese [mailto:edwardc@schoolph.umass.edu]
Sent: Monday, April 30, 2018 7:24 AM
To: Woods, Clint <woods.clint@epa.gov>
Subject: LNT obit

Clint:

See the article…..please share with your colleagues. It seems appropriate.

Ed

Message

From: Paula Goodhind [psg@umass.edu]
Sent: 5/29/2018 4:03:54 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: submitted comments
Attachments: Comments EPA-HQ-OA-2018-0259-0001_EPA-LNT Default-EPA 2.docx

Clint,

See the comments that I submitted last week to EPA. These submitted comments also contained about a dozen article PDFs as well.

Sincerely,

Ed

The EPA Cancer Risk Assessment Default Model Proposal: Moving Away From the LNT

Edward J. Calabrese, Ph.D.
Professor of Toxicology
Department of Environmental Health Sciences
Morrill I, N344
University of Massachusetts
Amherst MA 01003
Phone: 413-545-3164
E-mail: edwardc@schoolph.umass.edu

Jaap C. Hanekamp
Amundsenrede 7
2725GJ Zoetermeer
The Netherlands
Phone: 3179-346-0304
E-mail: hjaap@xs4all.nl

Dima Yazji Shamoun
University of Texas at Austin
Economics Department
2225 Speedway
BRB 2.102E, C3100
Austin, TX 78712
Phone: 512.471.3664
E-mail: dshamoun@utexas.edu

LNT – Its Corrupt History and Scientific Flaws

The proposal by the EPA (EPA, 2018) to no longer use the LNT as the default model in cancer risk assessment is correct and long overdue.[1] Given the present EPA proposal, its major challenge is whether a cancer risk assessment default model is needed, and, if so, what should it be? A default model in cancer risk assessment gets around the practical impossibility of testing agents for cancer risk over a large number of doses and with very large numbers of animals. This issue was well-demonstrated in the now famous FDA ED-01 study that utilized some 24,000 mice (Bruce, 1981). Such studies take too long, are too costly, and they reduce the possibility that other agents get tested since vast resources would be directed to the massively larger study(ies). In addition, the ED-01 study still could not explore the potential of very low risks without even a more substantial addition of mice.

Based on the history of chronic animal testing and the realization that large experiments were not practical, the National Toxicology Program (NTP) adopted the long-standing historical modus operandi of using the simple few/high doses approach to hazard assessment based on the inadequate assumption that the LNT model could make accurate predictions in the low dose zone. These few and excessively high doses, however, made it impossible to challenge the LNT predictions as a cancer risk assessment model. Thus, the NTP and the EPA worked together to create a system of evaluation in which the LNT model would become the default for essentially all animal model cancer risk assessments.

[1] Substantial criticisms of the historical and scientific foundations of the LNT model for cancer risk assessment have been published in the peer-reviewed literature as noted in these cited publications (Calabrese 2011, 2012, 2015b, 2017a-c). These publications show that the LNT was based on a flawed scientific foundation that were undetected within the scientific community until recently.

The history of EPA risk assessment regulations has been based either on epidemiological or animal model studies. In either case, knowledge of the nature of the response at low doses affecting normal humans is limited. For most regulated chemicals, adequate epidemiological studies don't exist and even "adequate" studies have important limitations. The reality of this situation has resulted in regulatory agencies, such as EPA, basing their human exposure standards on high dose/few dose animal studies with mice and rats, needing to extrapolate to humans, often across many orders of magnitude of dose (e.g. the history of volatile organic contaminants (VOC) regulation illustrates this point). The question is how does the EPA find a way out of this regulatory quagmire of using the historically corrupt and scientifically flawed LNT model? The answer is not in basing regulations on mechanistic in vitro studies as helpful as they are, nor on limited and inadequate epidemiological studies as useful as they are, nor on the few/high dose animal model approach. None of these approaches individually or collectively can offer a solution to the issue of cancer risk assessment.

An Improved Default Model Approach: Model Uncertainty

The best answer, for the foreseeable future, from theoretical data-support, and public health perspectives is the use of dose response model uncertainty, that is, using the leading dose response models and determining where they optimally converge to yield the so-called regulatory sweet spot. This "sweet spot" is the dose where health benefits are optimized and risks are minimized. The resultant of these converging science-driven processes will yield the optimal public health dose, with changes in dose going either up or down yielding less benefit/more public health harm, thus the sweet spot concept. In practice this involves finding a practical and scientific means to integrate the threshold, LNT, and hormetic dose response models, the three models with the most toxicological gravitas based on the peer-reviewed published literature.

Each model has its strengths and limits, its advocates and detractors. In the interest of full disclosure, the authors strongly favor the hormesis model and feel it is far superior to the threshold model and even more so to the LNT model (Calabrese, 2008; 2010; Calabrese et al., 2013). Nonetheless, it is argued here that the combination and integration of these three most substantial dose response models into a dynamic risk assessment framework works best because it has the potential to integrate the best scientific features of the three models while limiting/minimizing the possibility of error.

This process describes/predicts what happens if hormesis is correct or incorrect and the same for the LNT as these two models provide the bounds of harm or benefit. The case for this integrated dose response approach has been published in several peer-reviewed chemical and radiation health risk assessment publications (Calabrese, 2015a; Calabrese et al., 2015, 2016). Attractive features of this integrative approach are that the nadir of the hormetic dose response, based on a large number of studies in the hormetic data base (Calabrese and Blain, 2011), and the "safe" exposure estimate using the threshold dose response model with a standard 100-fold uncertainty factor yield essentially the same value. Thus, these two models provide an agreement, even though they offer a different toxicological interpretation (i.e. no effect/safe threshold interpretation versus beneficial hormetic interpretation). At this same dose, the LNT model was found to yield a cancer risk approximately 10-4 (or 1 per 10,000 people over an 80-year lifespan). This value represents a low risk within society, which is not detectable via epidemiological evaluation under the best of research conditions. It is also about 500-fold lower than the cancer risk from background (i.e. spontaneous tumors). Figure 1 provides a description of the integration of the threshold, LNT, and hormesis models within a model uncertainty framework, showing the optimized dose (i.e. the regulatory sweet spot). If the hormetic dose

response model predictions are correct, then the benefits to society in terms of disease reduction would be substantial. However, if hormesis was wrong and LNT is correct, the effects would be undetectable, again showing the regulatory sweet spot.

The integration of the three most credible scientific models within a model uncertainty suggests that more research still needs to be undertaken to improve the reliability of model-based low dose estimates. It also raises the possibility that this general approach might be able to be refined and fine-tuned so as to be applied to specific agents. For example, it is possible/likely that the hormetic optima may vary somewhat depending on the specific agent. Despite the remaining uncertainties of this proposed model uncertainty and dose optimization regulatory sweet spot approach, it offers considerable scientific and societal advances and should be adopted by the US EPA and other environmental regulatory agencies in other countries. It offers a strong scientific foundation, the integrated estimates of the three most evaluated models and it errs on the side of safety, while allowing society to capitalize on the potential of significant public health benefits. This perspective is far superior to the current LNT-default risk assessment both from scientific and public health perspectives. The EPA proposal should be accepted and implemented across all programs involving risk assessment as soon as possible.

Acknowledgement

EJC acknowledges longtime support from the US Air Force (AFOSR FA9550-13-1-0047) and ExxonMobil Foundation (S18200000000256). The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the author and should not be

interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to and where to submit for publication consideration.

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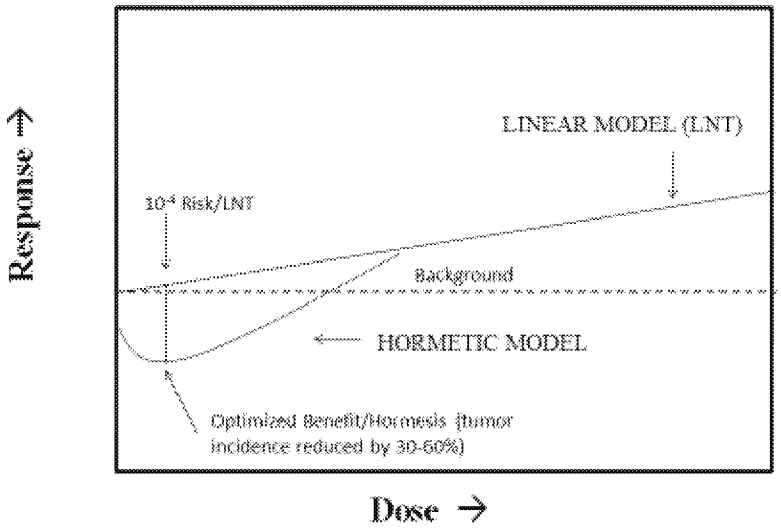
Figure 1. Integration of hormesis and LNT for risk assessment



Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 5/25/2018 5:11:13 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: RE: supporting the EPA proposal

Clint:

I will do this. However, it is on my secretary's computer and she is taking a long weekend....will send on Tuesday.
In addition, I have written a Commentary supporting it. It will be published in the journal Dose Response, which is indexed in all the major indices. The commentary is based on the comments but longer.
My comments also included the attachment of about a dozen published articles that support the submitted comments.

Ed

From: Woods, Clint <woods.clint@epa.gov>
Sent: Friday, May 25, 2018 1:06 PM
To: Edward Calabrese <edwardc@schoolph.umass.edu>
Subject: Re: supporting the EPA proposal

Thanks! Mind sending me a copy?

On May 25, 2018, at 1:01 PM, Edward Calabrese <edwardc@schoolph.umass.edu> wrote:

> Clint:
>
> Just to let you know I submitted my public comments strongly supporting the EPA proposal. This was done yesterday in a document that I co-authored with
> two colleagues.
>
> Sincerely,
>
> Ed Calabrese

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 5/29/2018 1:03:03 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Attachments: Environ. Pollut. Muller-Mech-1.pdf

Clint:

Question: The LNT story (see attached) is truly an amazing one.....it simply shows the horrible Foundation that cancer risk assessment was/is based on and how society is victimized by Fraud at the highest levels. Is this something that the EPA would be interested in developing a documentary on? This is really one of the next important steps forward.

Ed

Environmental Pollution 241 (2018) 289–302

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From Muller to mechanism: How LNT became the default model for cancer risk assessment☆

Edward J. Calabrese

Department of Environmental Health Sciences, Morrill I, N344, University of Massachusetts, Amherst, MA, 01003, USA

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Received 4 April 2018
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Ionizing radiation
Linear dose response
Threshold dose response
Mutation
Dose rate
Cancer risk assessment

ABSTRACT

This paper summarizes the historical and scientific foundations of the Linear No-Threshold (LNT) cancer risk assessment model. The story of cancer risk assessment is an extraordinary one as it was based on an initial incorrect gene mutation interpretation of Muller, the application of this incorrect assumption in the derivation of the LNT single-hit model, and a series of actions by leading radiation geneticists during the 1946–1956 period, including a National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel (Anonymous, 1956), to sustain the LNT belief via a series of deliberate obfuscations, deceptions and misrepresentations that provided the basis of modern cancer risk assessment policy and practices. The reaffirming of the LNT model by a subsequent and highly influential NAS Biological Effects of Ionizing Radiation (BEIR) I Committee (NAS/NRC, 1972) using mouse data has now been found to be inappropriate based on the discovery of a significant documented error in the historical control group that led to incorrect estimations of risk in the low dose zone. Correction of this error by the original scientists and the application of the adjusted/corrected data back to the BEIR I (NAS/NRC, 1972) report indicates that the data would have supported a threshold rather than the LNT model. Thus, cancer risk assessment has a poorly appreciated, complex and seriously flawed history that has undermined policies and practices of regulatory agencies in the U.S. and worldwide to the present time.

1. Introduction

While a role of the environment in affecting the occurrence of cancer has long been known (e.g., the occurrence of testicular cancer in chimney sweeps) (Pott, 1775), transitioning this recognition of concern into an experimental science proved to be difficult as seen in the series of failures to induce skin cancer in animal models during the early years of the 20th century. Finally, after many failed attempts, in 1918 Japanese researchers made the experimental breakthrough by the repeated administration of coal tars to the ears of rabbits to produce papillomas and carcinomas (Yamagiwa and Ichikawa, 1918). This seminal finding paved the way for experimental research to assess possible environmental causes of cancer.

In a similar manner, researchers early in the 20th century began to explore whether it was possible to induce mutations in plants and animals (Campos, 2015). While it took nearly three decades, Muller (1927a) reported that X-rays induced gene mutations in fruit flies, narrowly beating three independent teams of botanists who likewise reported inducing transgenerational phenotypic changes with X-rays/radium.[1] Muller's findings, like that of the Japanese cancer researchers, quickly transformed the field. For his discovery, Muller received the Nobel Prize in 1946. The current paper clarifies the historical foundations of the LNT single-hit dose-response model, its unique dependence upon the gene mutation interpretation of Muller in 1927, and how this interpretation became accepted by the scientific community and regulatory agencies. Most importantly, it will be shown that: (1) Muller's claim that the X-ray-induced transgenerational phenotypic changes were due to gene mutations was an interpretation lacking convincing evidence; (2) the induced transgenerational phenotypic changes

☆ This paper has been recommended for acceptance by B. Nowack.

E-mail address: edwardc@schoolph.umass.edu.

[1] In January 1927, in the *Proceedings of the National Academy of Sciences* (Communicated January 14, 1927), Gager and Blakeslee (1927) were the first to report cases of gene mutations. Thus, Muller's July 1927 publication was the second to report the gene mutation phenomenon. Muller gained acclaim because he produced many mutations quickly. However, Gager and Blakeslee repeatedly reminded the field of their primacy. In his effort to secure scientific honors, Muller (1927a, 1928a) failed to cite the earlier work of Gager and Blakeslee (1927).

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0269-7491/

were due to chromosomal deletions and aberrations, not Muller's proposed gene "point mutations"; (3) these developments undermine the historical and scientific foundations of the LNT single-hit model since it was built upon Muller's gene mutation interpretation (see Calabrese, 2017a for a significantly expanded analysis of this issue); (4) Muller and other leading U.S. radiation geneticists would collude in a series of articles to promote acceptance of the LNT, making deliberate deceptions and misrepresentations of the scientific record; (5) the deceptive practices would infiltrate and culminate in the actions of the U.S. NAS BEAR I Genetics Panel that recommended adoption of the LNT model by regulatory and public health agencies in 1956 (Anonymous, 1956) (See Calabrese, 2015a, b, c); (6) the mouse data used to provide the experimental basis for the subsequent reaffirmation of the LNT for cancer risk assessment was similarly problematic, that is, the BEIR I NAS/NRC (1972) Committee used a flawed historical control group that significantly overestimated risk in the low dose zone, yielding a linear dose response (see Calabrese 2017b, c); (7) use of a corrected historical control value yields a threshold rather than the linear dose response and; (8) this new assessment indicates that the LNT has been flawed from the start, yet national and international regulations have continued to be based upon it (Calabrese, 2015a, 2017d).

2. Muller and mutation

Hermann J. Muller, a radiation geneticist at the University of Texas/Austin, truly burst upon the national and international scene following his presentation at the 5th International Genetics Congress in Berlin during September 1927. His highly anticipated presentation convincingly demonstrated to an eager and massive grouping of geneticists from around the world that X-rays could induce transgenerational phenotypic changes in *Drosophila* perhaps providing a mechanism for evolution. Muller claimed that these changes were the result of induced gene mutation, tiny genomic changes, with Muller coining the term "point mutation". Muller not only claimed to be the first to ever artificially induce gene mutation, he produced copious numbers of them. Muller's presentation drew especially great anticipation since his article in the journal *Science*, published about three months earlier, only discussed some of the new findings, inexplicably failing to show any data. Thus, Muller, with a flair for the dramatic, disproved the doubters and set himself on a path that 19 years later would result in another trip to Europe, Stockholm, to receive the Nobel Prize in Biology and Medicine.

Muller's stunning results soon inspired: (1) numerous laboratories to redirect their research to the assessment of ionizing radiation induced mutations (Campos, 2015); (2) the creation of the Genetics Society of America (GSA) (1931) a few years later, bringing zoologists and botanists who were researching genetics under one integrated professional society; (3) the concept of a Proportionality Rule that describes the linear dose response for the ionizing radiation induced mutation response (Muller, 1930a); (4) the interdisciplinary collaboration of leading physicists and radiation geneticists to create the first mechanism-based cancer risk assessment model (LNT single-hit model) using target theory (Timofeeff-Ressovsky et al., 1935) and (5) the discovery of chemically induced mutations by Charlotte Auerbach in the 1940s (Auerbach and Robson, 1946). The reach of Muller was long and influential, inspiring the focus of Carson (1962) in her seminal book *Silent Spring*, that is normally given credit for starting the environmental revolution of the late 1960s and 1970s and continuing to the present. Muller wrote a powerfully supportive review of *Silent Spring* in the New York Herald Tribune published on the Sunday prior to the book's publication four days later (Muller, 1962). Thus, the X-ray induced "gene" mutation findings of Muller and his leadership over the next 40 years would profoundly affect the environmental movement and the fields of genetic toxicology, cancer risk assessment and numerous medical, radiation and public health practices.

There is therefore little question that Muller had a major influence on the scientific community and the general public, originating from the belief that he had actually demonstrated that X-rays produce gene mutations in the fruit fly. While the above summary highlights some of the societal impact of Muller, there are important parallel concerns with Muller's scientific legacy. In brief, Muller (1927a) made the critical assumption that the numerous X-ray induced transgenerational/heritable phenotypic changes that he reported were the result of induced gene mutations. Muller knew that transgenerational/heritable phenotypic changes via X-ray-induced chromosomal aberrations was not a significant finding (Muller, 1928b). This had been reported previously and would not affect an understanding of basic biological themes such as evolution and its potential mechanism. This was why Muller (1927a) entitled his groundbreaking July 22, 1927 article in *Science* "The Artificial Transmutation of the Gene".

3. Point mutations vs gene deletions

Within three months of his presenting these findings at the Genetics Congress[2] in Berlin (September, 1927) (Muller, 1928a), Muller (1927b) would publically express concerns that some might think that all he had done was to shoot large holes (i.e., deletions) throughout the genome with the high doses of X-rays used, noting that such concerns/questions were initiated by his longtime friend, close colleague, collaborator and confidante, Edgar Altenburg, a professor of genetics at Rice University. Within this anticipatory defensive context, at the December 1927 AAAS meeting at Nashville, Tennessee and in an April 1928 presentation to the U.S. National Academy of Sciences (NAS) Muller (1928b) tried to discount the possibility that his reported transgenerational phenotypic changes were due principally to heritable chromosome changes, suggesting as proof observations of reverse mutations (e.g., X-ray-induced reversible changes in eye color – red to white). Patterson and Muller (1930) would subsequently publish a massive 82-page paper supporting his argument. This was proof enough for Muller that X-rays induced small mutations in genes rather than vast and large deletions as suggested by Altenburg. Muller used apparent reverse mutation findings to preempt potential challenges to his gene mutation interpretation. Muller argued further that the assumed point mutations closely mimicked the type of gene mutation changes underlying the mechanism of evolution as might be seen with spontaneous gene mutations, spending much of the next

[2] The proceedings of this Congress contains Muller's paper, which included the data used for the basis of the Nobel Prize in 1946. The Congress proceedings paper of Muller had substantial limitations, being somewhat sloppily written, having three experiments, each with important weaknesses. It also lacked a methods section and provided no references, including no acknowledgement of the report by Gager and Blakeslee (1927) that preceded his *Science* paper (Muller 1927a) for the reporting of ionizing radiation induced gene mutation by six months. The general substandard quality of the manuscript made me wonder whether the Nobel Prize paper of Muller from the Congress proceedings had ever been peer-reviewed. A July 8, 1946 letter from Muller to Altenburg (Muller 1946a) revealed that the manuscript that he read at the Congress was exactly the same as published in the subsequent proceedings. Thus, it is virtually certain that the Nobel Prize research of Muller was not peer-reviewed (Calabrese, 2018). However, Muller had been acculturated into the need for and process of peer-review by Thomas Hunt Morgan, his Ph.D. advisor at Columbia University. Morgan helped to create the *Journal of Experimental Zoology* in 1903, which had a modern peer-review process from the start. In fact, Muller would publish several articles in this journal by 1920 (Harrison, 1945). Thus, Muller was part of a culture of peer-review as a necessity and expectation. Yet, he avoided it for the seminal findings for which he would be honored with the Nobel Prize.

Table 1
Stadler's challenge to Muller. quotes from Stadler (1932, 1954).

Stadler (1932). **Proc 6th Intern Cong Genet 1:274–294**
"To state that an induced variation is a gene mutation is not to explain it but merely to label it."
Page 274-275
"We do not demonstrate that a chemical change has occurred; we simply infer, since no mechanical explanation can be found, that the variation must be due to this invisible mechanism."
Page 275
"We may define mutation as a transmissible change in the gene. But we identify mutation by experimental tests, and these tests are not such as to establish conclusively, in specific instances, that a change within the gene has occurred."
Page 275
"In effect, any Mendelizing variation which cannot be shown to be due to a change involving more than one gene is a mutation."
Page 275
"… the occurrence of reversion is not proof that the original mutation could not have been due even to a deficiency."
Page 292
Stadler (1954). **Science 120(3125):811–819**
"But there was no test to identify mutations due to a change within the gene; it was simply inferred that the mutants that could not be identified as the result of specific mechanical causes were, in fact, due to gene mutation in the ideal sense (11)."
Page 813

40 years in this quest for a mechanism for evolution.

While these findings would temporarily satisfy the questioning and doubtful Altenburg and others, supporting the X-ray-induced point mutation interpretation, this concern would not go away but actually grew principally due to the persistent questioning and new research insights of the plant radiation geneticist Stadler (1932, 1954), Muller's most staunch, yet objective, respected, competitor and critic (Calabrese, 2017e).

4. Stadler challenges gene mutation interpretation

4.1. Cytogenetic advances

At the time of his groundbreaking mutation publication, Muller's (1927a) research suffered from an acknowledged limited cytogenetic evaluative capacity which prevented fine structure chromosome resolution ("… Drosophila cytology is elusive in its finer details" – page 721, Muller, 1928b), and thereby a reduced capacity to detect chromosomal deletions. Markedly improved chromosome cytogenetic resolution capacity was developed by the Cornell plant cytogeneticist, Barbara McClintock, in the prophase stage of meiosis with maize (McClintock, 1929). Two years later she would apply this novel technique to Stadler's X-ray treated corn in the summer of 1931. It revealed that what was once believed to be X-ray induced "gene" mutagens were sizeable chromosomal deletions. While these findings would force Stadler to re-evaluate and challenge his previously published X-ray induced "gene" mutational findings in barley (Stadler, 1928), they would make him raise the question of whether Muller's gene mutation interpretation with fruit flies was also incorrect. While Stadler would cautiously share his new doubts with the research community in several 1931 publications (Stadler, 1931a,b) and in private correspondence with leaders in plant genetics research like Karl Sax (Stadler, 1931c), Stadler (1932) would finally challenge the Muller gene mutation interpretation in a very public manner during his Plenary Address at the Sixth International Genetics Congress at Cornell University in the presence of Muller (Table 1).

From this opening round of public debate, Muller and Stadler would challenge each other over whether Muller had induced true gene mutations in his highly publicized high dose X-ray experiments. This research-generated debate would continue until the death of Stadler in 1954 (Stadler, 1954), involving numerous radiation geneticists trying to resolve this fundamental question (Calabrese, 2017a ; Lefevre, 1950; Voss and Falk, 1973). Copies of Stadler's research grants and interim reports to the U.S. NRC that describe his progressive series of multi-year research plans, research methods and experimental developments reveal a focused, high quality and productive research activity with numerous publications that challenged Muller's gene mutation interpretation (State Historical Society of Missouri, Stadler Papers). An extensive review of Muller's gene mutation hypothesis along with supportive and non-supportive literature findings is provided in the dissertation of Lefevre (1949), Stadler's Ph.D. student. In this instance Stadler would show his flair for excitement and self-confidence by directing his student (with the assistance of *Drosophila* specialists and with some formal assistance of Muller) to challenge Muller's gene mutation interpretation with Muller's own biological model. In this extensive study, Lefevre (1949, 1950) found no support for Muller's gene mutation interpretation based on reverse mutations.

To the outside viewer it suggested two outstanding scientists locked in a scientific dispute, with Muller compelled to protect his reputation, future, and legacy. These longstanding competitive research activities of Stadler and Muller were much like a high-level chess match in which all moves (e.g., research publications, professional society presentations) contributed important information. By the late 1930s and/or early 1940s Stadler and others had methodically shown that Muller lacked the needed proof for his gene mutation assertions (Calabrese 2017a). The subsequent development of improved cytogenetic staining for *Drosophila* chromosomes by Painter (1934) would reveal that the use of the very high X-ray doses and dose rates similar to Muller's key findings, like that of Stadler's research with barley and corn, produced copious chromosome aberrations including a high proportion of deletions, along with few, if any, possible gene (i.e., "point") mutations.

Muller's use of the reverse mutation concept was also found unconvincing as multiple papers showed several mechanisms (e.g., position effect) by which reverse transgenerational phenotypic traits could occur without any change in the gene[3] (Bedford and Dewey, 2002; Lefevre, 1950). Thus, every move that Muller made was seemingly countered by the research of Stadler or spin-off ideas his research had inspired. Furthermore, Stadler's and related publications would yield insights that were incrementally more definite, insightful and over time, more convincing than Muller's, much like forcing Muller into a corner.

[3] See the discussion from Lefevre (1949) dissertation for a detailed assessment of reverse mutation and position effect as related to Muller's gene mutation interpretation.

4.2. McClintock's new X-Ray induced mutation mechanisms

Complementing the Stadler gene mutation criticism were new mechanistic findings of Barbara McClintock's study with her breakfusion-bridge-cycle model of X-ray induced genetic damage (Comfort, 1997, 2001) which then led to strikingly new and transformative transposable element induced mutational insights. Her novel mutable gene concept was particularly attractive to Muller's University of Indiana Colleague and future Nobel Laureate Salvadore Luria (McClintock, 1948; Muller, 1948) as well as Muller's closest colleague and friend, Edgar Altenburg. In the case of Altenburg, he would devote much effort to understand the scientific foundations of McClintock's findings and its role in spontaneous and exogenously induced mutations. The McClintock discovery had very broad biological and biomedical implications. However, it would also take Altenburg back to his 1927 suggestion that Muller had been blasting large holes in *Drosophila* chromosomes by high dose X-ray treatments. Extensive and detailed correspondence between Altenburg and McClintock in the early 1950s reveal the significance that Altenburg placed on her findings and how it stripped much significance from Muller's gene mutation model.

Altenburg would repeatedly encourage Muller to study and assimilate the findings of McClintock (Altenburg, 1952a,b,c, 1953a). Altenburg would provide Muller with a 25-page manuscript on McClintock's transpositional element concept and its relationship to X-ray-induced mutations (Altenburg, 1953a,b). However, Muller (1953) claimed he was too busy to read the manuscript while also being dismissive, claiming that no one could understand the "jumping gene" (i.e., transposable element) concept (Altenburg, 1953a; Muller, 1953), a common technique to distract attention from a perceived competitor while protecting one's legacy. However, Muller was not successful in drawing Altenburg back into his sphere of dominance, but rather, Altenburg (1957) would devote an entire chapter to McClintock's mutable gene (transposable element) concept in the second edition of his Genetics textbook. Altenburg, an excellent writer, made the challenging writings of McClintock readily understandable for geneticists and interested biologists. In this chapter, he claimed that a substantial proportion of high dose X-ray-induced mutations are due to chromosome deletions/rearrangements rather than Muller's "point mutations" and that such genetic damage was likely mediated by transposable elements (Table 2). The profound intellectual transformation of Altenburg to the McClintock model was a significant sign that the era of Muller was waning. During this same period Russell et al. (1958) would publish his highly influential dose rate challenge to Muller. With multiple scientific challenges facing him, Muller would transform his laboratory into one that would try to extend the findings of Russell into *Drosophila* rather than exploring the dramatic and more complex new ideas of McClintock. Within a month of the Russell et al. (1958) publication Muller was exploring dose rate. In the six years of redirected and intense research on this topic Muller's laboratory was plagued with a series of apparent false starts and a generally ambivalent finish. Thus, the final years of Muller's laboratory productivity were weak, perhaps a function of aging and health deterioration (Calabrese, 2017b).

Of further importance, as suggested above, was the discovery by McClintock (1950, 1951, 1953) that transposable chromosomal elements affected the occurrence of both spontaneous and exogenously induced mutations, including mutations induced by ionizing radiation and chemical mutagens such as mustard gas as used by Auerbach with *Drosophila*. Subsequent findings indicate that the early X-ray-induced transgenerational phenotypic findings of Muller (1927a) and Timofeeff-Ressovsky et al. (1935) were likely the result of X-ray activation of McClintock's transposition element process which induced massive chromosomal damage, such as small to massive deletions and other types of chromosomal aberrations (Ratner et al., 2001). These collective developments served to strongly reinforce the fundamental criticisms by Stadler of Muller's gene mutation interpretation, while supporting the McClintock transpositional element mediated mutation model.

5. LNT single-hit model, dose rate and the Manhattan Project

While Muller was in serious dispute with Stadler throughout the 1930s for his gene mutation interpretation, there was nonetheless a worldwide mesmerizing euphoria of Muller's mutation discovery (see Campos, 2015), one element of which resulted in a unique interdisciplinary collaboration between leading physicists and radiation geneticists as led by Delbruck and Timofeeff-Ressovsky, respectively. From the mid-1930s their research provided the LNT model with a hypothetical mechanistic basis via the use of target theory (Timofeeff-Ressovsky et al., 1935). This concept was then transformed into a biostatistical model (i.e., LNT Single-Hit model) which revealed that the shape of the dose response in the low dose zone was largely a function of the assumed number of target hits required to produce a gene mutation (Zimmer, 1941). The fewer the hits needed to produce gene mutations the closer the linear dose response for gene mutation was approached.

Since his X-ray induced gene mutation interpretation had experienced serious scientific challenges and setbacks through the 1930s, Muller needed another approach to redirect the mutation debate to restore support for his gene mutation interpretation and low dose linearity model and their integrative linkage. Muller's idea was an intriguing one that served, at least in part, both purposes, with a new application of a "dose x time = constant" experiment as seen in the Bunsen-Roscoe Law or with Haber's Law. Over the decade of the 1930s using his Proportionality Rule Muller had asserted that X-ray induced mutation damage was progressively cumulative and could not be repaired. As a result of these characteristics the damage should be predicted by the total dose, not by dose rate. If the total dose hypothesis were true, then the dose response for mutation should be linear at low dose, all the way down to a single ionization. Muller would test this idea in a

Table 2
Quote from Altenburg E. (1957). Genetics. Holt, Rhinehart and Winston, New York, NY.

Are all mutations due to chromosomal rearrangements?

... The possibility, therefore, arises that mutations might often be due to invisibly small deletions, rather than to an actual change in a gene–a change that we refer to as a "point" mutation. We cannot be sure, for example, that the yellow body-color mutant in Drosophila has a "yellow" gene in place of a "gray" (the normal allele of yellow). For all we know, the body color of the mutant might be yellow because the normal allele has been deleted. In fact, yellow mutants of independent origin differ somewhat in the intensity of their yellow pigmentation and, in the case of certain "extreme" yellow, it is very likely that the mutation is due to a very small deletion. In general, there is no way of telling from the outward appearance of a mutant what sort of genetic change caused the mutation. Inversions and duplications are also known to have mutant effects–inversion because of a "position" effect, and duplications either for the same reason or because of the genic unbalance they cause.

Now deletions, inversions, and duplications are all the results of chromosome breakage and rearrangement. Therefore, in the present state of our knowledge, all mutations might conceivable be due to such rearrangement and not to any actual alteration in the gene itself."

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dissertation by Ray-Chaudhuri at the University of Edinburgh using X-rays and mature spermatozoa of *Drosophila*. The findings of this dissertation matched up very well with Muller's predictions supporting the total dose/LNT hypothesis. These results provided support at a critical stage to Muller's gene mutation theory. In fact, during Muller's (1946b) Nobel Prize lecture, he cited the research of Ray-Chaudhuri (1939, 1944).

The problem with this newly adopted dose-rate vs total dose strategy to defend the gene mutation interpretation was that the study of Ray-Chaudhuri had a series of important design and execution limitations, requiring corrections, improvements and replication (Calabrese, 2011, 2017a). In fact, there were so many limitations (e.g., limited sample size, quality control issues, changing animal models during the experiment, lacked documentation of essential methods, major statistical errors, failure to collect critical information), it suggested that the normally critical Muller might have lowered his academic standards in order to provide support to his sagging gene mutation interpretation.

The Ray-Chaudhuri dissertation in some ways served as a pilot study for the far more substantial efforts lead by Curt Stern, University of Rochester, during the Manhattan Project starting in 1943. Stern would initially direct an acute study by Warren Spencer, a highly regarded *Drosophila* specialist who was on leave from his faculty position at the College of Wooster (Ohio, USA). While the Spencer part of the study went as planned, a significant problem for Muller, a paid consultant on this project, occurred when the data from the low dose chronic genetic toxicity study, led by Ernst Caspari, revealed a significant dose-rate effect and a threshold for mutagenicity, contradicting the Ray-Chaudhuri (1939, 1944) conclusions. These findings by themselves had the potential to land a severe blow to the LNT single-hit theory. These findings were just preceded by 15 years of research lead by Stadler that successfully weakened the plausibility of Muller's gene mutation interpretation and now along with new mechanistic insights of McClintock on X-ray-induced mutations. This situation became sufficiently threatening to the policy goals of key leaders of the radiation genetics community such as Muller and Stern who strongly advocated the adoption of the LNT single-hit model. What happened next to the field of radiation genetics could not have been predicted.

The above set of events, which collectively placed the LNT single-hit model at risk, set the stage for what is referred to as "LNTgate" (Calabrese, 2015c, 2016, 2017d), a series of obfuscations, deceptions, and misrepresentations of the scientific record all designed to ensure that the LNT single-hit theory would replace the threshold model for cancer risk assessment. This sequence of events has been reported in detail over the past seven years via a series of progressively informed historical discoveries (Calabrese 2011, 2013, 2015a,b,d, 2016, 2017b,c,e).

The LNTgate actions were mediated via the leadership of Curt Stern and Hermann J. Muller during the second half of 1946, continuing for more than a decade. These efforts lead to the actions of the NAS BEAR I Genetics Panel to sustain and integrate these successful manipulations into the scientific record and government regulatory policies. These ideologically directed activities would be guided by the academic "offspring" of Muller and Stern, such as Jim Crow, Bentley Glass, and other esteemed leaders of the radiation genetics community. The process became fully successful when the next generation uncritically accepted as scientific fact, the mistakes, deceptions, and misrepresentations handed down by the icons of the field. This is, in fact, the domain where key features of the fields of regulatory policy and cancer risk assessment are today.

6. Saving the hit model

The LNTgate process had an unexpected spontaneous origin. It began when Ernst Caspari informed Stern, his supervisor, that his dose-rate findings contradicted those of Ray-Chaudhuri (total dose). As noted above, the observation of a threshold response for mutation was not only not expected but, as it turned out, actually "not permitted", resulting in Stern refusing to accept the Caspari findings (Calabrese, 2011). Giving the appearance of objectivity, Stern blamed Caspari's threshold "discovery" on the use of a faulty control group that he insisted was aberrantly high. Stern did not provide any evidence to support this critical judgment. However, Stern was aware of earlier publications with control group responses for this model that supported the Caspari interpretation based on prior correspondence (Stern, 1938), but he either forgot this or refused to share it. Regardless, the Caspari year-long study had reached an impasse with the Stern judgement, a major crisis.

Showing some degree of independence, Caspari would not accept Stern's judgement that his control group displayed aberrantly high values. He dove into the literature and found a series of papers, which explicitly addressed the control group question, with all supporting his position (Calabrese, 2011). When Caspari assembled these findings, Stern withdrew the control group criticism. During this period, Caspari informed M. Demerec, head of the Genetics Department for the Carnegie Institute, of his mutation threshold dose-response findings and the problems it was creating. This prompted the influential Demerec to write Caspari asking "what can be done to save the hit model" (Caspari, 1947). This statement seemed to express what Stern and Caspari might well have been thinking. With the control group issue no longer a viable means to discredit the Caspari findings, the "save the hit model" strategy of Stern became publishing the manuscript, but framing the discussion to prevent the data from being accepted/used, while still showing competence of the research team, thereby securing the LNT/Ray-Chaudhuri framework. This seemed like the best possible outcome for Stern and Caspari.

The strategy adopted was to assert that the Caspari data could not be accepted or used until it could be determined why he obtained a threshold in the chronic study, while Warren Spencer obtained an apparent linear dose response a year earlier in an acute study with the same fruit fly model while working under Stern. This created a false standard, as the two studies had more than 25 methodological differences; there would be no possible practical means to determine why the studies differed (Calabrese, 2011). The only way that this highly nuanced perspective (i.e., the recommendation not to use the Caspari findings until it resolved the differences with the Spencer study) could have been published was if Stern was the journal (i.e., *Genetics*) editor and there was no peer-review, and this was most likely just what happened (Calabrese, 2011)! In fact, even though Stern proposed this unrealistic situation, no one, of course, ever explicitly accepted this challenge over the next 70 years, including himself, Caspari or Muller. It was a tactical move in the broader strategy to "save the hit model". So Caspari and Stern prepared this manuscript with this obfuscation and sent it to Muller for review on November 6, 1946 with Muller answering on November 12, 1946 (Calabrese, 2011). Muller indicated that he was upset that Caspari found a threshold since this could be a serious problem for LNT acceptance and Stern needed to replicate the study (not to explain why the Caspari study differed from the Spencer study as emphasized in the discussion as this was impossible to do). Thus, Muller was fully informed that the strongest study (i.e., chronic exposure to ionizing radiation) to date (i.e., Caspari experiment) showed a threshold for mutation one month prior to the Nobel Prize lecture of December 12, 1946 (Muller, 1946b). The linearity supporting acute exposure experiment of Spencer had a series of methodological limitations (e.g. inadequate temperature control, inexplicably combining different dose-rate groups with the same total dose, inadequate X-ray machine

calibration) that affected the reliability of the low dose study results (Calabrese, 2011). Yet Stern, Muller and others never identified such limitations, even in Muller's detailed review of this research (Muller, 1946c). These criticisms of the Spencer study (Spencer and Stern, 1948), were first reported more than six decades later (Calabrese, 2011).

In his crucial moment of making scientific history, Muller (1946d) deceived the world with his statement that there is no possibility for a threshold response ("no escape from the conclusion that there is no threshold") to ionizing radiation induced mutation and that risks needed to be assessed via the LNT single-hit model (Nobel Prize lecture, Dec 12, Muller, 1946b). Muller made this statement having seen the Caspari study and not offering any technical or other criticism (Muller, 1946e). Thus, a type of collusion began to take shape between Stern, Caspari, and Muller to do as Demerec urged. In a follow up letter to Stern (Muller, 1947) Muller supported publishing of the Caspari paper since there were enough caveats (i.e., obfuscations) and restrictions to make the paper non-threatening to the LNT acceptance.

In 1949 Stern manipulated or colluded with the leadership of *Science* to ensure LNT would be strongly promoted (Uphoff and Stern, 1949). This was similar to how Muller (1927a) was treated two decades earlier showing no data on his Nobel Prize experiments nor seven years later (1956) in the journal's dealings with the fraudulent NAS BEAR I Genetics Panel publication (Anonymous, 1956). Here is how it happened. While the Stern research team hoped that the follow-up replication studies would put an end to the Caspari study-created crisis, it simply created a new one. The first replication experiment (i.e., led by a new master's student Delta Uphoff) was unacceptable to Stern, this time because the control group was aberrantly low. The control group's values were so outside the norm that Stern had to check with Muller who strongly affirmed (in writing) that the Caspari control group values were appropriate while rejecting Uphoff's (see Calabrese, 2015a,b for the letter correspondence documentation). The troubled Stern would go so far as to blame her for having been biased [i.e., "may reflect a personal bias of the experimenter" (Uphoff and Stern, 1947)], with this leading to the low control group values (Calabrese, 2015b). This phrase was stated in the Discussion of the manuscript that was sent to the Atomic Energy Commission (AEC) (and which was immediately classified). This amazing statement should have raised a plethora of questions by the scientific community for Stern and Uphoff but it was hidden from view. For example, how did the alleged bias start? How long did it continue? How might it have affected other experiments, other team members and others, the data analysis and manuscript write up? A follow-up experiment by Uphoff also suffered the same fate with an aberrant control group value. This situation was turning into a professional disaster. So the question was not just what could be done to save the hit model but also the reputations of Stern, Caspari, and Uphoff and other members of the Manhattan Project at the University of Rochester. Stern would again show his creativity (or deviousness). Since essentially no one had read the classified material discounting the results and blaming Uphoff and her alleged biases leading to the uninterpretable findings, Stern used his contacts with the journal *Science* to publish a one page technical note of the experiments of Spencer, Caspari, and Uphoff. In this limited technical note, Stern showed no transparency, neglecting to inform the reader that he had found the low control studies of Uphoff unacceptable less than a year before and now he concluded these findings were fully acceptable. No criticisms of the Spencer study were mentioned despite its obvious significant limitations (Calabrese, 2011). Stern also reintroduced criticism of the Caspari study without evidence. In this mini-meta analysis, Stern restored the LNT model, literally "saving the hit model". In the final paragraph, Uphoff and Stern (1949) promised the *Science* readers to provide a comprehensive paper with methods, materials, missing data and other relevant information. Yet, they never did.

Muller and Stern actually promoted the discredited findings of Uphoff while marginalizing the Caspari paper. More specifically, at the time Stern asked Muller to help resolve the Caspari-Uphoff control group issue, Muller had been studying spontaneous mutations in the fruit fly in his ongoing disputes with Stadler concerning whether he induced gene mutation (Calabrese, 2017a). Thus, Muller was sitting on a treasure trove of control group spontaneous mutation data. As noted earlier, in multiple letters to Stern, Muller unequivocally sided with the Caspari findings while rejecting those of Uphoff (Calabrese, 2015a, b). With this as prologue we now fast forward a few years and find Muller (1950, 1954a) rejecting the Caspari study based on this control group being abnormally high, contradicting the literature, his own data/publications and his multiple letters to Stern, while never providing proof for his statements. The evidence reveals Muller dishonestly strove to discredit the Caspari study, and preserve LNT, while protecting himself from being accused of lying during his Nobel Prize Lecture. The 1950 paper of Muller was just preceded and perhaps inspired by an article by MIT's Robley P. Evans in *Science* (Evans, 1949) criticizing the LNT model, using the threshold findings of Caspari (Caspari and Stern, 1948). After Muller read the Evans article, he wrote to Stern criticizing the paper of Evans, blaming the criticism of LNT on the findings of Caspari (Muller, 1949). Muller urged Stern to contact Evans and discredit the Caspari work. No evidence has yet been found that Stern communicated with Evans on this matter.[4] However, shortly after that letter exchange with Stern, Muller published his false criticisms of Caspari's control group. Furthermore, on August 10, 1949 Altenburg (1949) wrote Muller about the Caspari threshold findings, acknowledged the reliability of the findings yet in search of a mechanistic explanation. Apparently, Muller had thought that Stern and his efforts had fully neutralized the threshold findings of Caspari, but this was not apparently the case.

7. LNT and the NAS BEAR Genetics panel

The next stage of the LNT story would take place with the NAS BEAR I Genetics Panel which first convened in early November, 1955 at Princeton University. As Muller had learned from many earlier frustrations, success within Advisory Committees is highly dependent upon who is selected. In the case of the BEAR I Genetics Panel, the answer was clear from the start, as the Panelist Tracy M. Sonneborn, a Muller colleague at the University of Indiana, read their radiation geneticist mantra into the recorded proceedings with no debate or dispute. All firmly believed that mutational damage was cumulative and irreversible with the dose response being linear down to a single ionization. Multiple notable radiation geneticists at that time were not advocates of the Muller perspective but they were either directed to other NAS BEAR I panels such as was the case of Ralph Singleton (agriculture panel) or not selected as was the case of McClintock. In retrospect, the deck was stacked along with an administrative leadership that would keep the panel focused on the big picture goals of the Rockefeller Foundation (RF) that both funded and directed the Panel while in

[4] The papers of Evans have been preserved at MIT. However, they have yet to be organized for scholarly use and it is unknown when they will be available. Of interest would be whether Stern ever sent Evans the letter Muller suggested. A check of the Stern files at APS revealed no record of a letter of Stern to Evans.

the administrative structure of the NAS.[5]

Despite the endorsement of the LNT single-hit model by leading research geneticists and physicists it was widely recognized that the fundamental data to support the LNT single-hit model was inappropriate. The model was dependent on point mutations, not large deletions, gene rearrangements, and other gross aberrations. In his final and masterful paper, published posthumously in *Science*, Stadler (1954) would illustrate how Muller's mutational data could not provide a credible biological basis for the LNT single-hit model. Despite the prominence of the journal *Science*, the stature of Stadler and the timeliness of the article, this criticism of the LNT single-hit model was never discussed by the NAS BEAR I Genetics Panel. In fact, not once in the transcribed pages of the Panel meetings were Stadler or McClintock's research on gene mutation ever mentioned.

At the second meeting of the Panel (in Chicago), Warren Weaver, Chair of the Genetics Panel and Director of Research for RF, tried to entice members of the Panel with RF funding if the Panel Report would support RF initiatives (e.g., LNT). Weaver indicated he would "try to get a very substantial amount of free support for genetics if at the end of this thing we have a case for it. I am not talking about a few thousand dollars, gentlemen, I am talking about a substantial amount of flexible and free support to geneticists" (Anonymous, 1956 - BEAR I Genetics Panel Transcript, February 5, 1956, page 35).[6] Weaver would further state that "There may be some very practical results – and here is the dangerous remark – don't misunderstand me, we are all just conspirators here together". The Weaver remarks obviously link the Panel deliverables to RF funding for geneticists, including those sitting in the room. Further discussions of the Panel during the February 5/6, 1956 meeting would reveal that to be successful in the eyes of Weaver, the Panel would need to present strong agreement/consensus for the estimation of genetic risks to the U.S. population assuming a linear dose response. However, an unanticipated problem came about 4–5 weeks later (March 1956) when the Panel members displayed multiple profound disagreements: they argued about whether it was possible to even estimate population risks, how to derive the estimations, how any derived estimates of damage related to true (real) risks, and what the risks actually were. With this confusion, the highly divergent results of the independent risk estimates that were carried out over 10 generations were seen as an unusable scientific "mess", such that Panel member, Jim Crow, would claim that no one would believe the policy recommendations of the Panelists since they could not agree amongst themselves. In a March 29, 1956 Letter to Warren Weaver, Crow (1956) stated that:

> "The limits presented on our estimates of genetic damage are so wide that the readers will, I believe, not have any confidence in them at all."

Lacking authority to do so, Crow, who was to organize the technical reports for Panel discussion, decided to arbitrarily drop the three lowest estimates of risk; by so doing he markedly reduced the variation, giving the false impression of more expert Panelist agreement than was the case. Even after dropping the three, there remained considerable uncertainty, being still too large to show to the scientific community and general public. One might have thought that the Panelists whose estimates were dropped would have strongly fought to have them retained. There is some evidence of significant disputes between Demerec and Muller on this matter based on a letter from Muller to Beadle in August 1956 (Muller, 1956) indicating that Muller did not want to be part of writing a scientific justification for their LNT recommendation. He indicated that he was already too frustrated with his debates with Demerec over the value of *Drosophila* versus bacteria in their risk estimations and did not want to air the so-called dirty laundry in public. He had thought that they had agreed to disagree. However, the available record does not reflect the details of this matter, as it likely occurred in the March 1956 meeting once Crow received the detailed write-ups for which there was no meeting transcript. Muller also noted his unresolved debates with the human geneticists of the Panel further confirming his unwillingness to seek a consensus report justifying their scientific recommendations. This lack of blatant open dispute/rebellion suggests that the group consensus was to present a united front that Weaver had earlier pointed out was necessary, perhaps using this funding carrot to achieve agreement. However, panelist James Neel, who refused to provide an estimate, strongly disputed the legitimacy of the proposed genetic damage estimation activity (Neel 1956 a, b). He argued that any consensus agreement was an illusion based on a self-fulfilling decision to reduce variability by forcing the use of similar models with similar process assumptions. Even with Crow stacking the deck, the risk estimates were still too variable, leading Weaver and Crow to encourage/coerce the Panel not to show their range of estimates to the outside world since it would destroy their credibility. The Panel would keep it private. There was no "minority" report nor leaking to the media. The "control" of the group was evident as those such as Demerec and Neel would not publically challenge the group view despite fundamental differences.

8. The NAS BEAR I Committee Genetics panel *science* publication story

The BEAR I Genetics Panel published a major article in *Science* (Anonymous, 1956) on their findings and recommendations. This paper had three significant misrepresentations of the Panel's research record. The first involved the Panel stating that the 12 geneticists of the Panel were invited to provide estimates of genetic risks for the entire U.S. population exposed to a certain dose of ionizing radiation, but only six accepted the challenge and provided the write up. Yet, nine of the 12 actually did, with Crow dropping three estimates as noted earlier.[7] In fact, I had obtained the nine detailed assessments. Second, the *Science* paper indicated that the minimum and maximum estimates of genetic damage range was ±10 or 100 fold. However, the actual average minimum-maximum damage range was about 750 fold. Third, the Genetics Panel *Science* paper neglected to report that three Panelists refused to participate, principally because they believed that such estimates could not be reliably done.

A written record exists that documents that the NAS BEAR I Committee Genetics Panel voted not to share their data with the scientific community and others (Calabrese, 2015a). After the Panel's publication in *Science* it was specifically challenged by

[5] Dr. Detlev Bronk was President of the Rockefeller Institute for Medical Research (later named Rockefeller University) and President of the National Academy of Sciences (NAS) during this time, confusing the roles of the Rockefeller Foundation and the NAS in this BEAR I Genetics Panel process.

[6] The concept of self-interest science (i.e., exaggerating fears of radiation to enhance research funding) of some members of the BEAR I Genetics Panel was documented via uncovered correspondence (Calabrese, 2014).

[7] It is interesting to note that the three estimates that Crow dropped (i.e., Demerec, Wright, and Kauffmann) were the areas with which Muller (1956) acknowledged serious issues in his letter to Beadle. Since Muller and Crow had a very close professional and personal relationship, it is tempting to speculate that Muller may have influenced Crow to drop the three estimates. This perspective is attractive since it is doubtful that Crow, one of the youngest members of the Panel, would have acted so precipitously without significant senior backup support. This would have been especially the case if he were doing Muller's bidding. Further documentation will be need to evaluate this hypothesis.

several leading U.S. academic researchers to share the scientific basis for the report and again the Panel formally voted not to do this as well (Calabrese, 2015a). Of significance is that the Panel had never even written such a scientific basis for their LNT recommendation. This should be seen as failed leadership by the NAS President Detlev Bronk and Chairman Weaver, a sign of scientific arrogance, or a type of defense posture. The Panel vote during August, 1956 not to provide a scientific basis for this major recommendation to adopt the LNT single-hit model for risk assessment was then passed on to NAS president Bronk, who accepted their decision. The NAS administration was therefore fully complicit in this process (Calabrese, 2015a).

The NAS BEAR I Committee Genetics Panel therefore falsified the research record, creating a significant cover up. Providing a detailed write up of their process would have revealed the deliberate misrepresentations of the research record. It would also have revealed a highly embarrassing fundamental lack of competence by such prestigious leading geneticists who simply could not properly address this risk estimation problem, as highlighted by Crow's amateurish and incorrect response (Calabrese, 2015a, b). It would also have taken considerable effort to complete such a report, something that should have been done during the activity of the Panel.

The goal of the NAS BEAR I Genetics Panel was to recommend adoption of the LNT in the U.S. and worldwide. Within about two years the LNT recommendation was adopted by national and international advisory committees, eventually becoming worldwide policy for cancer risk assessment. Thus, the most significant policy recommendation for cancer risk assessment lacked a written scientific basis. Most striking is that the Panel, including Muller, and the president of the NAS made this decision. It is ironic that the U.S. National Committee for Radiation Protection and Management (NCRPM) adopted LNT for cancer risk assessment in December 1958, based on the documentation-lacking NAS BEAR I Genetics Panel report days prior to the publication of Russell et al. (1958) demonstrating the existence of dose rate for ionizing radiation in the mouse model. Apparently, the status of the Genetics Panel and the NAS was so high that no documentation was needed for governments worldwide to adopt their transformative recommendations. As recently noted by Calabrese (2017a), seven of the members of the highly prestigious NAS BEAR I Committee Genetics Panel had no research experience with the effects of ionizing radiation on mutations. In fact, Crow, who had never published on the topic, made the decision on which estimates to retain. It is also ironic that Demerec and Neel, who were amongst the most appropriately experienced, did not contribute to the radiation risk estimates. Thus, the vision that the country was being guided by the most prestigious and experienced grouping of geneticists on the matter of radiation induced genetic damage was yet another myth to enhance acceptance of the LNT.

9. LNT, William Russell and the dose rate challenge

Within 2.5 years of the June, 1956 NAS BEAR I Genetics Panel *Science* publication, another *Science* publication would challenge one of the basic tenets of the BEAR I, Genetics Panel's recommendations. The paper was by William L. Russell of the Oakridge National Laboratory, also a member of the NAS BEAR I Genetics Panel. During June and July of 1958 Russell's group (Calabrese, 2017a, b) made a major discovery, that dose-rate, not total dose, was the key predictor of ionizing radiation induced mutation for mouse spermatogonia and oocytes. The Oak Ridge group kept this breakthrough discovery quiet, not presenting the findings at the International Genetics Congress in Burlington, VT in the middle of August. Russell did share the findings with a New York Times reporter during the Conference who wrote an article (Schmeck, 1958). The breakthrough paper was published on December 19, 1958 and with it was a timed release front page story by a Pulitzer Prize journalist (i.e., Nate Finney) for the Buffalo Evening News who specialized in atomic energy (note that the NY Times was then on strike) (Finney, 1958; Russell et al., 1958).

The Russell research revealed that damage from ionizing radiation was not cumulative, but reversible and had the potential to yield a threshold, suggesting the existence of DNA repair, a possibility that Altenburg shared with Muller soon after publication of the paper (Altenburg, 1958). In effect, Russell had discredited the mantra of the radiation geneticist community, creating a major problem. His strategy would be to promote the acceptance of his research while, at the same time, creating an impression of adhering to the radiation geneticist mantra. Russell did not want to be ostracized and marginalized from his field by his ideological radiation geneticist peers. Russell had seen the dominating and uncompromising personality of Muller in action many times while a member of the Genetics Panel (Crow, 1995) and with James Neel, whose paper Muller tried to prevent from being presented at an international genetics conference during the summer of 1956. In fact, Russell's supervisor, Alexander Hollaender, negotiated a follow up "reconciliation" meeting between Neel and Muller (January 1957) at Oakridge, essentially in the presence of Russell (Neel, 1956a, b; Neel, 1957a, b; Novitski, 1956) (Table 3). Thus, Russell knew only too well how hostile Muller could get if one deviated from the radiation genetics ideology. Russell would walk this dose-response tight rope until after the death of Muller in April 1967, after which Russell would unleash a profound set of criticisms of the radiation genetics mantra and the LNT concept (Russell, 1969, 1973).

Despite these findings, their massive expansion by Russell and their powerful challenge to the LNT single-hit recommendation of BEAR I, it would take some 14 years before a new powerful NAS Committee, now called the BEIR I Committee with the Genetics Subcommittee being chaired by Muller's protégé Jim Crow to reconsider the LNT recommendations of BEAR I. During this process the BEIR I Genetics Subcommittee re-examined the BEAR I report and made two clear initial determinations (Calabrese 2017a,b). The first was that the risk assessment recommendation of BEAR I (Anonymous, 1956) needed to be based on a mammalian model rather than on a fruit fly. The second factor was their acknowledgement that the BEAR I Genetics Panel (Anonymous, 1956) made a mistake in denying dose-rate. The recognition that dose-rate rather than the total dose best predicted mutation damage, meant that the radiation geneticist belief of cumulative and irreversible damage with each dose would be replaced. This finding also meant that linearity may be at risk of being replaced by the threshold dose response, reversing the 1956 position of the BEAR I Genetics Panel. However, despite these new challenges to the LNT model, the Genetics Subcommittee still had a strong disciple of Muller in charge with Crow[8] and would find some rationale to keep the linear dose response model as the default if possible.

Even though the findings of Russell revealed a true threshold for oocytes, the same could not be said for spermatogonia, where the dose-rate related damage, which was mediated by DNA repair, was only able to reduce total mutations induced acutely by 70% and not the 100% needed to achieve a threshold (Figure 1). The BEIR I Genetics Subcommittee therefore concluded that even though it was now known that an ionizing radiation threshold existed for mouse

[8] Toward the end of his career, Crow would acknowledge that Muller and he were amongst the strongest advocates of LNT and that they were too extreme in their views and actions (Crow, 1995).

Table 3
Quote from Neel (1959) letter to Beadle, September 14, 1959.

"There is no mind in science today for whose brilliance I have greater respect than that of Dr. Muller. In the first upsurge of concern concerning the effects of the increasing exposure of the human species to the radiation which followed World War II, it was Muller who had thought most about the problem, and Muller whose point of view dominated the picture. When Jack Schull and I pulled together our monograph on the findings in Japan, we felt obligated to try to fit these findings into the context of present knowledge. The outgrowth of that attempt, our Chapter 15, was a number of questions concerning Muller's argument. We couldn't prove that he was wrong, but we didn't feel he could prove that he was right. In other words, we felt that there were a number of unvalidated assumptions behind a good many of his points. One aspect of this evaluation of ours was a little critique of the significance of mutation rate studies. This critique I delivered at the WHO Study Group on the Effect of Radiation on Human Heredity which met in Denmark in the summer of 1956. I regarded it as part of the normal scientific interchange, but Dr. Muller apparently regarded it as an attack upon his life's work. There developed a rather strained relationship which persists until the present day, I am afraid, and keeps coming back to me in small ways which I consider beneath the dignity of a great man. Be that as it may, Alex Hollander was Chairman of that meeting in Denmark. Muller apparently insisted to Hollander that my statements were unacceptable and should be modified, to the point where Hollander arranged a meeting between Muller and myself at Oak Ridge, in an effort to reconcile the differences of opinion. At this point a number of the British participants in the WHO Study Group got wind of what was afoot, through no efforts of my own, and got their own backs up. It so happened that they agreed with my point of view and in effect transmitted the message that if any pressure were brought upon me, they would withdraw their own papers."

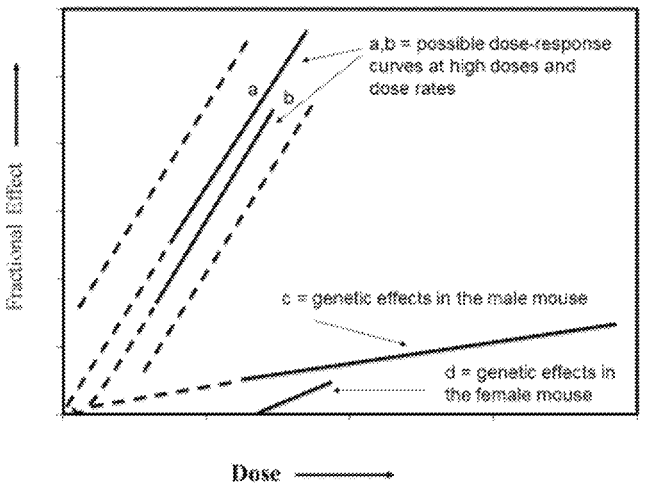

Figure 1. BEIR dose rate graph 1972. Hypothetical dose-response curves for leukemia and genetic effects (Source: NAS/NRC 1972 – page 98). Solid line = observed. Dashed extension of solid lines = unobserved. Line "a" and "b"; possible dose-response curves at high doses and dose rates. Parallel dashed lines = rough limits of error for lines a and b. Lines c and d represent genetic damage in the male and female mice, respectively.

oocytes, the LNT would be based on responses of the mouse spermatogonia. While this logic was convincing to the Genetics Subcommittee one would have to wonder why this didn't require further evaluation. Could there be an evolutionary explanation for why oocytes might show a threshold while spermatogonia didn't? Do oocytes have a more efficient DNA repair system than spermatogonia? Are responses of reproductive cells directly applicable to somatic cells?

These above noted questions were not explored or debated by the BEIR I Genetics Subcommitee. The point here is that the Genetics Subcommittee failed to broadly consider the question and were directed by the Crow leadership to obtain the desired outcome. Thus, Crow and his Genetics Subcommittee retained the LNT based on the non-threshold mutation data of the mouse spermatogonia. These views were accepted by a non-inquisitive U.S. EPA in 1975 and reaffirmed in 1977 all with reference back to the Russell research (Calabrese, 2017c).

The findings of Russell were critical for modelling cancer risk assessment for ionizing radiation based on the Atomic Bomb Survivor data for cancer outcomes. However, these epidemiological findings have limited detectability at low doses (Taubes, 1995), and findings need to be extrapolated toward background exposure. In this key low dose extrapolation process the assumption of linearity was made by the BEIR I Genetics Subcommittee (NAS/NRC, 1972) with the findings of Russell serving as the biological dose-response "homing" device for the LNT model. In the late 1970s the U.S. EPA directly extended this linearity model based on ionizing radiation to chemical carcinogens (Albert et al., 1977). The EPA linear cancer risk assessment policy would be challenged in 2017 when Calabrese (2017b,c) reported that the Russell historical control had been found in error (Selby 1998a, b), and had been corrected for a massive error in 1996 by the Russells (Russell and Russell, 1996). Calabrese showed that if the corrected historical data had been used by the BEIR I (NAS/NRC, 1972) Genetics Subcommittee the male mouse would have shown a threshold while the female would show an hormetic response. These findings indicate that the basis for the LNT assumption was incorrectly formulated and that the adoption of LNT for risk assessment was incorrect.

10. Discussion

The present paper reveals that Muller did not discover what he claimed, that is, the "artificial transmutation of the gene" and this finding challenges the validity and application of the LNT single-hit model for cancer risk assessment (Calabrese, 2017a; Crow and Abrahamson, 1997). Muller was also incorrect on the issue of dose-rate (Russell et al., 1958) which had a significant impact on acceptance and promotion of the LNT single-hit theory (Calabrese, 2017b,c). Although complex, Muller's career was fundamentally centered on his quest to be the first to produce gene mutations, and then to defend this interpretation the rest of his life, against the findings of Stadler (1931a, b, 1932, 1954) and others and then over the remaining six years of his research career (1959–1964) on the issue of dose-rate (Calabrese, 2017a, b), while trying to avoid the alternative gene mutation model of McClintock (1950, 1951, 1953) and its advocacy by Altenburg (1957).

Current scientific understandings, therefore, reveal that Muller could not sustain the conclusion that his high dose X-ray induced artificial transmutations of the gene were "real" gene mutations. The strong preponderance of evidence in the 1930s suggested chromosome level heritable genetic changes based on advances in cytogenetic staining, findings that have been confirmed with nucleotide sequencing technologies (Calabrese, 2017a). Since Muller was incorrect with his gene mutation interpretations the LNT single-hit theory of Timofeeff-Ressovsky et al. (1935) lacked a scientific relationship with the data that was used as its foundation (as pointed out by Stadler, 1954). Despite being wrong on the fundamental biological issues, the Muller-led faction of the radiation genetics community was successful in achieving the adoption of LNT worldwide. This was largely due to its highly organized radiation geneticist network focus, profound exaggeration of risks, and collusions with the Rockefeller Foundation and the U.S. NAS (Calabrese, 2013, 2015a,b,d), and their massive LNT-promotion campaign immediately following BEAR I which affected

government, the scientific community, the media and the general public.

Since the deceptions (e.g., BEAR I) and significant errors (e.g., BEIR I) can be traced back to major scientific historical figures, Nobel Prize winners (i.e. Hermann Muller, George Beadle and Max Delbruck), prestigious U.S. NAS Committees (i.e. BEAR I and BEIR I) and at least one past NAS president (i.e. Detlev Bronk) (Calabrese, 2015a, b), it is important that the ideological history of cancer risk assessment in the U.S. be documented and become a part of the scientific and regulatory agency historical record to help ensure that vital public health policies and practices do not continue to be the offspring of a scientifically incorrect and dishonest past.

This historical assessment reveals a complicated dynamic amongst researchers, their colleagues, and rivals, all within a framework of politics, policies, social philosophies and personalities. Hermann Muller led the field, starting with redefining the concept of mutation and finding improved ways to assess it. Muller worked on these matters within a framework of wanting to be first, gaining recognition and its benefits and pushing this to extremes. One example of this obsession is seen when Muller claimed credit for an important discovery (i.e., first reported in *Drosophila* in which both genetic and cytological evidence of translocation were combined) that Curt Stern had made (Muller, 1929a, b; Muller and Painter, 1929; Stern 1926, Stern, 1929a, b). This resulted in getting the normally reserved Stern to confront Muller via correspondence. Muller was forced to publically apologize and correct the matter. However, symptomatic of this behavior and in this same general period, Muller would apparently manipulate an editor at *Science* to publish his discussion on X-ray induced mutation without providing any data, simply doing so as a means to ensure that he would be first - a tactic that was enormously rewarded.

Much of what Muller did over the next four decades was to preserve and defend the legacy of his breakthrough gene mutational findings/interpretation and the formulation of the Proportionality Rule (the LNT concept). In so doing, Muller would become the intellectual leader of the radiation genetics community, helping to ensure its importance and create new professional and funding opportunities. The principal challenge for Muller was the thoughtful reflections of Stadler and his capacity to create and test key hypotheses, the data from which would challenge Muller's interpretation of his "groundbreaking" findings. Stadler, who was unrelenting, objective and insightful, seemed to follow in the footsteps of Muller's Ph.D. advisor T.H. Morgan. These researchers, according to Muller (1946f), "abhorred what they termed "speculation", that they even distrusted the validity of the most essential lines of reasoning." Stadler and Morgan were leaders in that wave of skepticism whose participants "doubted the doubt 'til they doubted it out." (Muller, 1946f). In the end, Muller's interpretations were revealed via such follow up experimentation to be incorrect, that is, the very high doses he used produced heritable chromosomal, not gene, phenotype changes. More than 50 years later, with advances in nucleotide assessment methods, it would be shown that ionizing radiation could produce some gene mutations but at far lower doses (Asakawa et al., 2013; Colussi et al., 1998; Colussi and Lohman, 1997; De Serres, 1991; De Serres et al., 1967; Fossett et al., 1994; Furuno-Fukushi et al., 2003; Liu et al., 2003; Mognato et al., 2001; Nakamura et al., 2005; Nelson et al., 1994, 1995; Nohmi et al., 1999; Okudaira et al., 2010; Park et al., 1995; Russell and Hunsicker, 2012; Schwartz et al., 2000; Sudprasert et al., 2006; Thacker, 1986, 1992; Thacker et al., 1990; Toyokuni et al., 2009; Webber and De Serres, 1965; Yamada et al., 1996).

Muller loyalists, such as Charlotte Auerbach (1976) and others, would strain the limits of credibility by arguing that Muller was proven to be correct. These examples of revisionist history were based on an incorrect interpretation of his findings. Muller would excite the world with the claim he produced 40 gene mutations one weekend afternoon, more than the entire field had produced in a decade (Carlson, 1981). Yet, we now know that he was not producing gene mutations. In fact, Auerbach (1978) would eventually support Stadler noting that "Stadler tested many X-ray mutations of a particular gene in maize and found that all of them were deficiencies. Not long ago this conclusion was confirmed by experiments on a different gene in maze. Muller's evidence, gained from work with *Drosophila*, was less direct …" (Auerbach, 1978). While Auerbach (1978) gave the proverbial nod to Stadler's perspective, this was done even more emphatically by two very close colleagues and friends of Muller. Crow and Abrahamson (1997) acknowledged that Stadler's deletion interpretations had been convincingly supported with modern analytical methods and that Muller was simply too stubborn, holding on too long to a discredited position. However, old deeply held and self-serving beliefs such as Muller's original error of interpretation, would mesmerize the scientific community making it impossible to change, as it became an accepted myth leading to the creation of the LNT single-hit model for cancer risk assessment, affecting vast changes in public health risk assessment policies and risk communication strategies, while being susceptible to political and ideological manipulation.

The Muller story reveals a conflicted character, the discoverer of an apparent major breakthrough, something that he greatly desired. At the same time, Muller was tortured with the possibility that he was wrong, spoke too soon, that his mutations were really only holes that the X-rays had poked in the chromosomes. He knew only too well that if his mutations were really only poked holes there really wasn't much new or great with his "breakthrough" discovery. Thus, we have a life that sought to "hold on", while trying to prove that he actually had produced "real" mutations.

Eventually the scientific story of Muller's chromosomal rather than gene mutations would progressively emerge, even if it would take up to five decades after he received his Nobel Prize. The influence of Muller continues to be dominantly reflected in current regulatory policy, which was based on poorly formulated science, in need of corrective transformation by major agencies, such as the U.S. EPA, which however have been unable or unwilling to do.

The story of Muller's discovery of gene mutation also speaks to the broader issue of science being self-correcting. Due to the courage and focus of Stadler, Muller's interpretations were challenged and tested in the laboratory. This inspired others, including perhaps a desperate Muller, to seek the truth.[9] These challenges would be tested in the domains of cytogenetics, position effects, transpositional elements, reverse mutations, and eventually with the use of the Southern Blot, PCR and other DNA technologies. We now know that Stadler was correct when he said that it was critical for the scientific community not to confuse the observation of transgenerational phenotypic changes at high doses with its unknown mechanism(s). In the end, Muller was trying in 1927 to discover the mechanism of evolution, and he "knew" that it must be gene mutation. However, he convinced the world (at least for a while), and maybe himself, that he had done so with his high dose *Drosophila* experimentation. However, the scientific community can thank Stadler and his collaborator McClintock for creating the necessary doubt that would eventually lead to science displaying a self-correction for Muller's claim. An important follow up question is whether regulatory agency "science", like that of experimental science, can be self-correcting. Now many years after Muller's

[9] In private letters with Altenburg (Altenburg, 1953c; Muller, 1953; 1954b,c), Muller would acknowledge problems with his reverse mutation explanation, the significant role of position effect and the influence of the mutable genes of McClintock.

incorrect interpretations were revealed, society still lives with a risk assessment model based on a mistaken set of Muller's interpretations. In 1995 Crow would reflect upon the impact of his generation of radiation geneticists in estimating ionizing radiation induced risks. With his then 20-20 hindsight Crow stated that Muller's leadership and action "oversold the dangers, and should accept some blame for what now seems, to me at least, to be an irrational emphasis by the general public and some regulatory agencies on low-level radiation ….."

In the aftermath of the BEIR I (1972) recommendation and the adoption of the LNT perspective for regulatory agency policy and practice came a spate of biostatistical models offering estimates of cancer risk in the low dose zone following the linearized perspective. The broad range of linearized models were highly speculative attempts to estimate risks at very low doses often using some feature of enhanced biological plausibility, such as the number of theoretical stages in cancer development, the role of interindividual variation, the incorporation of carcinogen bioactivation and DNA repair and other approaches (Cornfield, 1977; Crump et al., 1976; Hoel et al., 1975; Krewski and Brown, 1980; Rai and Van Ryzin, 1981). This type of modeling started, for the most part, in 1961, with the Mantel and Bryan paper, based on the carcinogen contamination Cranberry scare during the Kennedy-Nixon election of 1960 followed by a hiatus until the mid-1970s after the creation of EPA and OSHA when legislative and regulatory activities intensified. These models were constrained by linear assumptions as provided by the BEAR I Genetics Panel, the BEIR I Committee and the official adoption of LNT from BEIR I in 1975 by EPA [see recommendation to support the LNT single-hit model by a subcommittee of the U.S. Department of Health & Welfare (Hoel et al., 1975)]. In between these two NAS committees there were many advisory groups of a national and international nature that followed BEAR I (Calabrese, 2013, 2015a). The linear assumption of these models in the mid-1970s and later were based on the predecessor NAS committees, with BEIR I having the latest and most direct impact since it was based on mice rather than fruit fly model of BEAR I. Given the above historical reconstruction, the risk assessment modeling activities would have been considerably different had EPA determined that the default should be a threshold or hormetic model. The rapid dominance of linear cancer risk assessment modeling in the late 1970s would not have occurred without the recommendations of the two NAS committees. These modeling activities were derived from biostatisticians who tried to derive more biologically motivated linearized models, not being aware of the plotting, scheming, deceptions, misrepresentations and mistakes of the two NAS committees. In the end, the real leaders were Muller, his radiation geneticist followers and their institutional partners. The subsequent linearized modeling was simply the following of the linearity script as written by the NAS BEAR I Genetics Panel.

These convergent entities reached a type of critical mass during the NAS BEAR I Committee Genetics Panel, facilitating no less than a scientific, social, psychological and politically-based risk assessment revolution within the U.S. and essentially all other countries adopting the LNT model for cancer risk assessment.

11. Conclusions

1. Muller incorrectly assumed he induced gene mutations in 1927 when he demonstrated that X-rays induced transgenerational phenotypic changes in *Drosophila* (Calabrese, 2017a).
2. The Muller findings had a major impact on the scientific community. His non-peer-reviewed data (Calabrese, 2018) and incorrect interpretations were widely accepted (Campos, 2015).
3. This incorrect gene mutation mechanistic interpretation lead to the development of the "Proportionality Rule" for dose response in 1930 by Muller and the LNT single-hit dose response model in 1935 by Timofeeff-Ressovsky et al. (Calabrese, 2017a).
4. Muller's gene mutation interpretations were strongly challenged in the genetics community, especially by Lewis J. Stadler and Barbara McClintock, who showed that Muller's gene mutation interpretation lacked scientific proof and could be explained by other mechanisms (Calabrese, 2017a).
5. Limited research directed by Muller supported a conclusion that X-ray induced mutations were best explained by total dose, not dose rate and the genetic damage was cumulative, irreversible and the dose response was linear (Ray-Chaudhuri, 1939,1944)
6. Muller's total dose findings were strongly challenged in Manhattan Project research with far stronger studies (Calabrese, 2011a). These findings were improperly marginalized by leaders of the U.S. radiation genetics communities including Stern and Muller who misrepresented the data via deceptions, false statements and obfuscations (Calabrese, 2011a, 2015b, 2016).
7. The inappropriate awarding of the Nobel Prize in 1946 to Muller for producing "gene" mutations gave an enormous credibility to the LNT risk assessment model, facilitating its acceptance within the scientific, medical, regulatory and political communities. It is likely that the award had long lasting societal impact that facilitated worldwide acceptance of LNT.
8. It was incorrectly assumed by the scientific/regulatory communities and prestigious advisory groups (e.g. U.S. NAS BEAR I Committee, Genetics Panel) (Anonymous, 1956) in the late 1950s that the responses of mature spermatozoa to ionizing radiation induced "gene" mutation which were linear at high doses and independent of dose rate and such doses could be generalized to all cell types, doses and dose rates (Calabrese, 2015b, 2016).
9. These assumptions were incorrect because it was later (i.e. early 1960s) determined that mature spermatozoa lacked DNA repair, thereby preventing its capacity to repair radiation and chemically induced mutation as could occur in somatic cells (Calabrese, 2017b, c).
10. The NAS BEAR I Genetics Panel deliberately misrepresented their own research findings and hid their contradictory findings to promote the acceptance of the LNT model for regulatory agency risk assessment (Calabrese, 2015b, 2016).
11. William L. Russell at the Oak Ridge National Laboratory starting in late 1958 demonstrated that ionizing radiation induced mutations in mouse spermatogonia and oocytes were dependent upon dose-rate, not total dose as had been assumed, due to their capacity to repair DNA damage (Calabrese, 2017b, c).
12. The BEIR I (NAS NRC, 1972) Genetics subcommittee acknowledged the "mistake" of the NAS BEAR I Genetics Panel on dose-rate but still retained the LNT recommendation because the significant reduction in mutation rate in the spermatogonia as shown by Russell et al. had not regressed to control values as in oocytes. Nonetheless, the BEIR I Genetics Subcommittee suggested that findings from spermatogonia had greater capacity for generalization to somatic cells, due to repair capacities, as compared to mature spermatozoa. Russell referred to failed DNA repair capacity as an "odd phenomenon, restricted to spermatozoa and

occasioned by the peculiar nature of the specialized spermatozoan cell." (Calabrese, 2017b,c)

13. Selby (1998a,b) in 1995 detected a significant error in the Russell mouse specific locus test historical control group. This error was subsequently acknowledged and corrected by Russell and Russell (1996) along with Selby (1998a,b). If this error had not been made or had been corrected prior to the creation of BEIR I the mouse spermatogonia data that was used to support continuance of the LNT model would have supported a threshold or hormetic model based on the Russell and Selby corrections, respectively (Calabrese 2017b,c).
14. Summary: The LNT for cancer risk assessment originated due to (1) a critical mistake by Muller that he had discovered X-ray induced "gene" mutation, (2) the adoption of the LNT single-hit model was based on this assumption, (3) a mistake in generalizing the use of the DNA-repair deficient mature spermatozoa for somatic cells by BEAR I (4) deceptions and misrepresentations of the scientific record by leaders of the radiation genetics community, including the NAS BEAR I Genetics Panel and (5) failure to detect the error in the Russell Mouse Specific Locus Test control group, which would have precluded support for LNT. EPA then extended the error by adopting LNT for cancer risk assessment, stating in 1975 and 1977 that it was based on the now recognized erroneous dose rate findings of Russell as cited in BEIR I (1972).
15. It is ironic that the misrepresentation of the scientific record by this NAS BEAR I Genetics Panel to promote their ideological agenda stands in sharp contrast to the memorialized quote on the Einstein statute on the very grounds of the U.S. NAS in Washington, DC. It states: "The right to search for truth implies also a duty; one must not conceal any part of what one has recognized to be true." As the historical record shows the NAS BEAR I Genetics Panel did not follow the guidance of Einstein.

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Conflict of interest

The authors declares no conflict of interest.

Declaration of interest

None.

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Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 6/7/2018 8:56:25 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: new paper
Attachments: Muller Nobel-Peer Review.pdf

Clint:

See the new paper.

Ed

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 7/24/2018 9:10:12 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: EPA proposal

Clint:

I will be publishing a Commentary in the journal Dose Response that strongly supports the EPA proposal. It should should be available for free on the journal website and listed in Pub Med and other leading data bases. I will send it to you ASAP.

Ed

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 5/26/2018 9:10:14 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: new LNT paper
Attachments: Environ. Pollut. Muller-Mech-1.pdf

Clint:

See new LNT paper as of this morning!!

Ed

Message

From: McClintic, Howard [McClintH@ctc.com]
Sent: 4/27/2018 2:38:16 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: Agreeing with the Controversial Transparency Rule
Attachments: ATT00001.txt; FINAL one page LNT project summary 10-24-17.docx; FINAL LNT Presentation of Howard McClintic.pptx

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2711 Jefferson Davis Hwy,, Suite 620
Arlington, VA 22202
(703) 310-5688 (703) 310-5655
FAX
at
(202) 689-4586 Mobile
E-Mail: McClintH@ctc.com

Good Morning Mr. Woods,

My colleague, Dr. Robert (Bob) Golden and I knew that this Transparency Rule was coming and cheer its arrival – Bravo!

Nonetheless, I am haunted when I read the Administrator's urging: that the rule **be lasting**! There is ***only one way*** for this important tectonic change to meet and that is it **be mandated** by a newly formulated, independent Committee of the National Academy of Sciences (NAS). When undertaking their literature review, the NAS Committee Members and Staff will uncover a recently released, peer reviewed, highly credentialed, science-based Report that makes plain that there is a wealth of

toxicological and epidemiology data for chemicals and radiation that will readily yield reproducible as well as transparent regulations.

Administrator Pruitt is unique in recognizing that the mathematical construct that the EPA uses for assessing risk, the linear no-threshold (LNT) methodology, is of **MOST** questionable scientific validity. The LNT model was originally adopted by the National Academy of Sciences (NAS) in 1956 for radiation and in 1977 for chemicals. Because LNT-driven regulations, whether for chemicals or radiation, have, for many years, been claimed to be science-based (see (https://science.house.gov/sites/republicans.science.house.gov/files/documents/HHRG-113-SY-20131114-SD001%20.pdf as well as http://www.c-span.org/video/?327016-1/epa-administrator-gina-mccarthy-testimony-proposed-regulations), the underlying scientific foundation for such regulations, particularly the LNT model itself, should also, by definition, reflect empirical data. If such scientific data are lacking, as they are for the LNT model, science-based regulatory methodologies (including benefit-cost analyses) for both chemicals and radiation should be updated to reflect significant advancements in scientific knowledge.

Besides introducing you to the fact that the ***CTC Foundation*** has empaneled a prestigious Science Committee that comprised of 15 individuals in the fields of toxicology, radiation biology, evolutionary biology, epidemiology, risk assessment, and economics; the Committee is preparing its FINAL Report that will demonstrate that there is no scientific support for the LNT model

and that ample modern data (NOT threshold models) should be the bases for regulations. In particular, the abundant data generated as part of the Department of Energy's 10 year, $200 million Low Dose Radiation Research Program (LDRRP) will be a central element of the anticipated publication. Collectively, these and other complementary data have elucidated the cellular defense mechanisms by which humans can withstand exposure to low dose radiation without adverse effects.

I have begun to encourage the "doctors in the US Senate" (Barrasso [R-WY] and Cassidy [R-LA]) to introduce and progress legislation in the Senate that would be a companion bill to H.R. 4675, pertaining to the low dose radiation research that Doctor and US Congressman Roger Marshall (R-KS) championed. There are some modifications that Dr. Robert (Bob) Golden and I would advocate, given our respective professional experiences working at NAS, but more on that later. Our overarching Goal is shared: a paradigm shift whereby a **lasting**, scientifically valid approach for radiation and chemical risk assessment as well as for economic benefit-cost analyses be achieved.

Thank you for your time and interest.

Most sincerely yours,

Howard

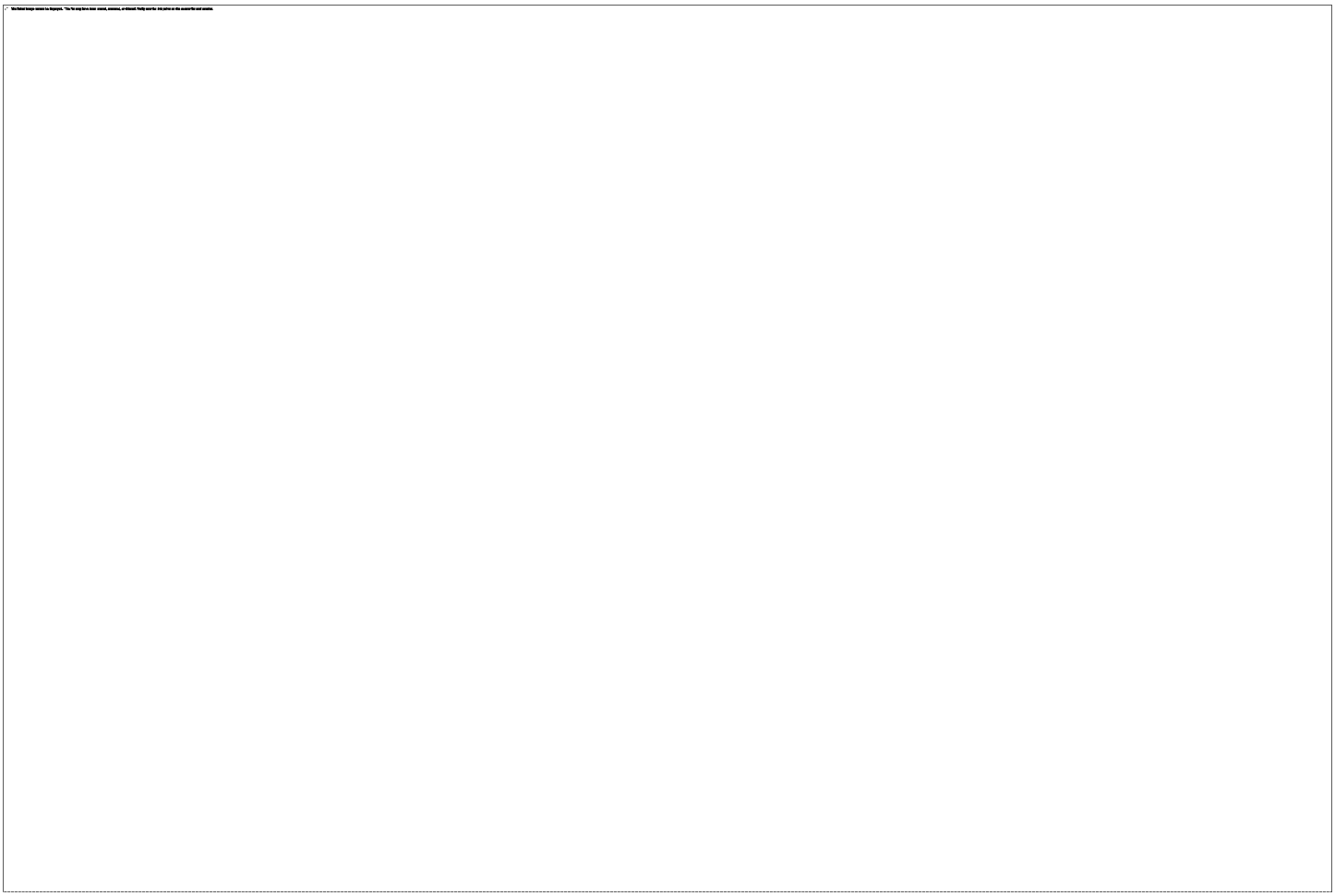
Howard G. McClintic
Executive Director

202 689 4586

https://www.washingtonpost.com/news/energy-environment/wp/2018/04/24/pruitt-to-unveil-controversial-transparency-rule-limiting-what-research-epa-can-use/?noredirect=on&utm_term=.4f5c21b67c8c

Pruitt unveils controversial 'transparency' rule limiting what research EPA can use

by Juliet Eilperin and Brady Dennis by Juliet Eilperin and Brady Dennis Email the author
Energy and Environment
April 24 at 6:09 PM Email the author



Environmental Protection Agency chief Scott Pruitt listens to President Trump address reporters before a meeting at the White House this month. (EPA-EFE/Shutterstock)

This post has been updated.

Environmental Protection Agency Administrator Scott Pruitt moved Tuesday to limit what science can be used in writing agency regulations, a change long sought by conservatives.

The proposed rule would only allow the EPA to consider studies where the underlying data is made available publicly. Such restrictions could affect how the agency protects Americans from toxic chemicals, air pollution and other health risks.

Pruitt and proponents describe the new approach as an advance for transparency, one that will increase Americans' trust and

confidence in the research on which EPA decisions are based. "Today is a red-letter day," he told a group of supporters at agency headquarters. "The science that we use is going to be transparent. It's going to be **reproducible**."

But a chorus of scientists and public health groups warn that the rule would effectively block the EPA from relying on long-standing, landmark studies on the harmful effects of air pollution and pesticide exposure. Such research often involves confidential personal or medical histories or proprietary information.

The move reflects a broader effort already underway to shift how the EPA conducts and uses science to guide its work. Pruitt has upended the standards for who can serve on its advisory committees, barring scientists who received agency grants for their research while still allowing those funded by industry.

His announcement Tuesday came as the administrator faces increasing heat for ethics and management decisions — from both sides of the political aisle, with even President Trump privately voicing more concern over the growing number of allegations. Pruitt only focused on the proposed rule during his remarks, saying his agency was "taking responsibility for how we do our work and respecting process."

He made clear he intends the new requirements to be lasting ones. "This is not a policy," he said. "This is not a memo."

The proposal will be subject to a 30-day comment period, EPA officials said. Scientific organizations are already campaigning to

block the rule from being finalized. Based on previous court cases, it could prompt legal challenges if implemented.

Former EPA administrator Gina McCarthy said that requiring the kind of disclosure Pruitt envisions would have disqualified the federal government from tapping groundbreaking research, such as studies linking exposure to leaded gasoline to neurological damage or a major 1993 study by Harvard University that established the link between fine-particle air pollution and premature deaths.

Scientists often collect personal data from subjects but pledge to keep it confidential. Researchers will have trouble recruiting study participants if the rule is enacted, she predicted, even if they pledge to redact private information before handing it over to the government.

“The best studies follow individuals over time, so that you can control all the factors except for the ones you’re measuring,” said McCarthy, who now directs the Center for Health and the Global Environment at Harvard’s public health school. “But it means following people’s personal history, their medical history. And nobody would want somebody to expose all of their private information.”

House Science Committee Chairman Rep. Lamar Smith (R-Tex.), who was with Pruitt during his announcement Tuesday, has for years sought to establish a similar requirement. His 2017 legislation, titled the Honest and Open New EPA Science Treatment Act, failed to pass both chambers.

Pruitt and Smith met at EPA headquarters on Jan. 9, according to Pruitt's public calendar, and an email obtained under the Freedom of Information Act indicates that the lawmaker pressed the administrator to adopt the legislation's goal as his own.

Smith made "his pitch that EPA internally implement the HONEST Act [so that] no regulation can go into effect unless the scientific data is publicly available for review," Aaron Ringel, deputy associate administrator for congressional affairs at the EPA, wrote other agency staffers. His email was obtained by the Union of Concerned Scientists, a scientific advocacy organization.

Conservatives, such as Trump EPA transition team member Steve Milloy, have long tried to discredit independent research the agency used to justify limiting air pollution from burning coal and other fossil fuels. A series of studies has shown that fine particulate matter, often referred to as soot, enters the lungs and bloodstream and can cause illnesses such as asthma and even premature death.

"During the Obama administration, the EPA wantonly destroyed 94 percent of the market value of the coal industry, killed thousands of coal mining jobs and wreaked havoc on coal mining families and communities," Milloy said in a statement, "all based on data the EPA and its taxpayer-funded university researchers have been hiding from the public and Congress for more than 20 years."

While the administration presses ahead, legal experts warn that the rule may be vulnerable to a court challenge. In unanimous decisions in 2002 and 2010, the U.S. Court of Appeals for the

District of Columbia Circuit said the EPA is not legally obligated to obtain and publicize the data underlying the research it considers in crafting regulations.

In the 2002 case, brought by the American Trucking Associations, two judges appointed by Ronald Reagan and one named by Bill Clinton wrote that they agreed with the agency that such a requirement "would be impractical and unnecessary." The government's defense had noted that "EPA's reliance on published scientific studies without obtaining and reviewing the underlying data is not only reasonable, it is the only workable approach."

A range of scientific organizations are already campaigning to block the rule from being finalized. On Monday, 985 scientists signed a letter organized by the Union of Concerned Scientists, urging Pruitt not to forge ahead with the policy change.

"There are ways to improve transparency in the decision-making process, but restricting the use of science would improve neither transparency nor the quality of EPA decision-making," they wrote. "If fully implemented, this proposal would greatly weaken EPA's ability to comprehensively consider the scientific evidence across the full array of health studies."

Under the proposed rule, third parties would be able to test and try to replicate the findings of studies submitted to the EPA. But, the scientists wrote, "many public health studies cannot be replicated, as doing so would require intentionally and unethically exposing people and the environment to harmful contaminants or recreating one-time events."

Gretchen Goldman, an expert on air pollution and research director for the organization's Center for Science and Democracy, said the rule could put some scientists in a quandary: Keeping personal health data or propriety information private would mean having their work ignored by the EPA.

"We have this incredible science-based process that works, and it has worked, by and large, even in the face of tremendous political pressures to not go with a science-based decision," Goldman said.

The Environmental Protection Network, a group of former EPA employees, issued a report Tuesday stating that many older studies — in which the original data sets were either not maintained or stored in outdated formats — would be eliminated under the proposed rule.

And while there is no estimate yet for how much it would cost EPA to obtain and disseminate studies' underlying data, the Congressional Budget Office has projected that Smith's measure, if enacted, would cost the agency $250 million for initial compliance and then between $1 million and $100 million annually. A 2015 CBO analysis estimated that EPA would cut the number of studies it relies on by half because of the bill's requirements.

Geophysicist Marcia McNutt, who is president of the National Academy of Sciences, said Tuesday that she is concerned the rule would prevent the EPA from relying on the best available scientific evidence.

"This decision seems hasty," she wrote in an email. "I would be fearful that the very foundations of clean air and clean water could be undermined."

Yet the American Chemistry Council praised Pruitt's effort. "Our industry is committed to working with EPA to help ensure the final rule increases transparency and public confidence in the agency's regulations," its statement said, "while protecting personal privacy, confidential business information, proprietary interest and intellectual property rights."

Joel Achenbach and Dino Grandoni contributed to this report.

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 10/22/2018 5:59:56 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: new paper
Attachments: Muller-Nobel Prize-1.pdf

Clint:

See my latest on Muller/LNT.

Ed

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 8/10/2018 9:01:35 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: see new paper on EPA proposal
Attachments: Dose Response-Model Uncertainty.pdf

Flag: Flag for follow up

Clint:

See the attached new paper....published overnight.

Please distribute to your colleagues.

Ed

Commentary

Dose-Response:
An International Journal
July-September 2018:1-4

DOI: 10.1177/1559325818789840
journals.sagepub.com/home/dos
SAGE

The EPA Cancer Risk Assessment Default Model Proposal: Moving Away From the LNT

Edward J. Calabrese[1], Jaap C. Hanekamp[2], and Dima Yazji Shamoun[3]

Abstract

This article strongly supports the Environmental Protection Agency proposal to make significant changes in their cancer risk assessment principles and practices by moving away from the use of the linear nonthreshold (LNT) dose–response as the default model. An alternate approach is proposed based on model uncertainty which integrates the most scientifically supportable features of the threshold, hormesis, and LNT models to identify the doses that optimize population-based responses (ie, maximize health benefits/minimize health harm). This novel approach for cancer risk assessment represents a significant improvement to the current LNT default method from scientific and public health perspectives.

Keywords

cancer risk assessment, model uncertainty, LNT, hormesis, threshold, dose–response, US EPA

Linear Nonthreshold—Its Corrupt History and Scientific Flaws

The proposal by the Environmental Protection Agency (EPA)[1] to no longer use the linear nonthreshold (LNT) as the default model in cancer risk assessment is long overdue. It has been extensively documented that: (1) The LNT model has been based on flawed science (ie, Hermann J. Muller never induced point mutations but rather large gene deletions and other gross chromosomal aberrations[2]; (2) the LNT model has incorrect scientific interpretations (ie, Muller incorrectly assumed that his transgenerational phenotypic changes in Drosophila were due to gene mutations)[2]; and (3) the LNT single-hit theory has been formulated under the incorrect assumption that the, Muller X-ray induced gene mutation theory was sound.[3]

Further, the history of LNT has been ripe with deliberate misrepresentations of the scientific record, including (1) the incorrect dismissal of the Caspari threshold findings by Stern and Muller (see study by Calabrese[4]) contradicting a copious research record and substantial private correspondence between Muller and Stern[4]; (2) Muller's powerfully influential comments in his Nobel Prize Lecture were deliberately deceptive[5,6]; (3) scientific misconduct by the entire membership of the US National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel which lead to governmental adoption of the LNT (ie, publishing deliberately false information in the journal *Science* to enhance the acceptance of LNT; NAS BEAR I Genetics Panel, 1956[4,7]); and (4) serious errors on mutation risks that were introduced into the key Biological Effects of Ionizing Radiation (BEIR) I Report in 1972[8] which were adopted by the EPA in 1975 to justify the adoption of LNT for chemicals and radiation.[9,10]

It is only recently that the BEIR I mistakes and their perpetuation to the present by other US NAS BEIR Committees and their risk assessment implications were reported. The LNT cancer risk assessment policy, procedures, and belief system are based therefore upon a newly recognized series of corrupt actions and mistakes by key national leaders principally in the radiation genetics domain. These controlling deceptions and

[1] Department of Environmental Health Sciences, University of Massachusetts, Amherst, MA, USA
[2] Science Department, University College Roosevelt, Middelburg, The Netherlands
[3] Economics Department, University of Texas at Austin, Austin, TX, USA

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Corresponding Author:
Edward J. Calabrese, Department of Environmental Health Sciences, University of Massachusetts, Morrill I, N344, Amherst, MA 01003, USA.
Email: edwardc@schoolph.umass.edu

errors have guided the US cancer risk processes from the mid-1950s to the present. As important as these documented errors and deceptions for the LNT model are, a vast scientific literature exists that refutes the low-dose predictions of the LNT model.[11-13,22] Also, LNT falls outside the empirical, as no experiment would actually be possible to causally connect the perturbation of some part of the DNA by 1 ionizing photon/1 genotoxic molecule that subsequently would develop, over the organism's lifetime, into some disorder such as cancer. Linear nonthreshold simply assumes this by default.[14]

Given the present EPA proposal, its major challenge is whether a cancer risk assessment default model is needed, and, if so, what should it be? A default model in cancer risk assessment gets around the practical impossibility of testing agents for cancer risk over a large number of doses and with very large number of animals. This issue was well demonstrated in the now famous Food and Drug Administration ED-01 study that utilized some 24 000 mice.[15] Such studies take too long, are too costly, and they reduce the possibility that other agents get tested, since vast resources would be directed to the massively larger study(ies). In addition, the ED-01 study still could not explore the potential of very low risks without even a more substantial addition of mice.

Based on the history of chronic animal testing and the realization that large experiments were not practical, the National Toxicology Program (NTP) adopted the long-standing historical modus operandi of using the simple few/high doses approach to hazard assessment based on the inadequate assumption that the LNT model could make accurate predictions in the low-dose zone. These few and excessively high doses, however, made it impossible to challenge the LNT predictions as a cancer risk assessment model. Thus, the NTP and the EPA worked together to create a system of evaluation in which the LNT model would become the default for essentially all animal model cancer risk assessments.

The history of EPA risk assessment regulations has been based either on epidemiological or on animal model studies. In either case, knowledge of the nature of the response at low doses affecting normal humans is limited. For most regulated chemicals, adequate epidemiological studies don't exist, and even "adequate" studies have important limitations. The reality of this situation has resulted in regulatory agencies, such as EPA, basing their human exposure standards on high dose/few dose animal studies with mice and rats, needing to extrapolate to humans, often across many orders of magnitude of dose (eg, the history of volatile organic contaminants regulation illustrates this point). The question is how does the EPA find a way out of this regulatory quagmire of using the historically corrupt and scientifically flawed LNT model? The answer is not in basing regulations on mechanistic in vitro studies as helpful as they are, nor on limited and inadequate epidemiological studies as useful as they are, nor on the few/high-dose animal model approach. None of these approaches individually or collectively can offer a solution to the issue of cancer risk assessment.

An Improved Default Model Approach: Model Uncertainty

The best answer, for the foreseeable future, from theoretical data support and public health perspectives is the use of dose–response model uncertainty, that is, using the leading dose–response models and determining where they optimally converge to yield the so-called regulatory sweet spot. This "sweet spot" is the dose where health benefits are optimized, and risks are minimized. The resultant of these converging science-driven processes will yield the optimal public health dose, with changes in dose going either up or down yielding less benefit/more public health harm, thus the sweet spot concept (note 1). In practice, this involves finding a practical and scientific means to integrate the threshold, LNT, and hormetic dose–response models, the 3 models with the most toxicological gravitas based on the peer-reviewed published literature. Each model has its strengths and limits, its advocates, and its detractors. In the interest of full disclosure, the authors strongly favor the hormesis model and feel it is far superior to the threshold model and even more so to the LNT model.[16-18] Nonetheless, it is argued here that the combination and integration of these 3 most substantial dose–response models into a dynamic risk assessment framework works best because it has the potential to integrate the best scientific features of the 3 models while limiting/minimizing the possibility of error.

This process describes/predicts what happens if hormesis is correct or incorrect and the same for the LNT as these 2 models provide the bounds of harm or benefit. The case for this integrated dose–response approach has been published in several peer-reviewed chemical and radiation health risk assessment publications.[4,19,20] Attractive features of this integrative approach are that the nadir of the hormetic dose response, based on a large number of studies in the hormetic database,[11] and the "safe" exposure estimate using the threshold dose–response model with a standard 100-fold uncertainty factor yield essentially the same value. Thus, these 2 models provide an agreement, although they offer a different toxicological interpretation (ie no effect/safe threshold interpretation versus beneficial hormetic interpretation). At this same dose, the LNT model was found to yield a cancer risk approximately 10^{-4} (or 1 per 10 000 people over an 80-year lifespan). This value represents a low risk within society, which is not detectable via epidemiological evaluation under the best of research conditions. It is also about 500-fold lower than the cancer risk from background (ie, spontaneous tumors). Figure 1 provides a description of the integration of the threshold, LNT, and hormesis models within a model uncertainty framework, showing the optimized dose (ie, the regulatory sweet spot). If the hormetic dose–response model predictions are correct, then the benefits to society in terms of disease reduction would be substantial. However, if hormesis was wrong and LNT is correct, the effects would be undetectable, again showing the regulatory sweet spot.

The integration of the 3 most credible scientific models within a model uncertainty suggests that more research still

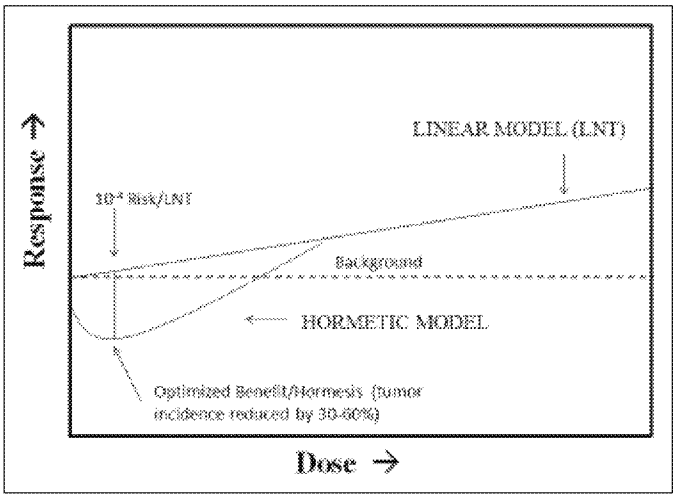

Figure 1. Integration of hormesis and LNT for risk assessment. LNT indicates linear nonthreshold.

needs to be undertaken to improve the reliability of model-based, low-dose estimates. It also raises the possibility that this general approach might be able to be refined and fine-tuned so as to be applied to specific agents. For example, it is possible/likely that the hormetic optima may vary somewhat depending on the specific agent. Despite the remaining uncertainties of this proposed model uncertainty and dose optimization regulatory sweet spot approach, it offers considerable scientific and societal advances over the present LNT model and should be adopted by the US EPA and other environmental regulatory agencies in other countries. It offers a strong scientific foundation, the integrated estimates of the 3 most evaluated models and it errs on the side of safety, while allowing society to capitalize on the potential of significant public health benefits. This perspective is far superior to the current LNT-default risk assessment both from scientific and from public health perspectives. The EPA proposal should be accepted and implemented across all programs involving risk assessment as soon as possible.

Authors' Note

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Note

1. It is worth noting that the "optimal dose" or the "sweet spot" proposed in this article is only based on the dose–response science in cancer risk assessment. A work in progress by Dima Shamoun and Richard Williams expands on this idea of optimal dose by marrying economic analysis (in the form of benefit–cost analysis) with dose–response modeling. The idea is that the optimal dose occurs where the marginal cost is equal to the marginal benefit of the reduction in dose. This *economically* optimal dose would take into account regulatory costs, various administrative costs, compliance costs, and risk–risk trade-offs and health–health trade-offs. As a result of this comprehensive calculus, the economically optimal dose may occur at a dose higher than the optimal dose proposed here yet maximizing the net benefits of a risk-based regulation. See, for example, Keeney.[21]

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Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 4/25/2018 3:19:36 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]

Clint:

If possible please send me the EPA statement that we worked on.....

Ed

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 4/25/2018 8:55:28 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: follow up

Clint:

I did see publicity yesterday on the new initiative. I will look forward to receiving the official document.
Let me ask. Does this change open up the possibility to reassess the many environmental standards that were based on the LNT model in the area of drinking water, superfund clean up procedures and the broader range of EPA risk based decisions. Back in the 1990s I developed the air toxics program for Rhom and Haas Chemical Company (now part of Dow). Such a project would be very different with this greater flexibility, I suspect/hope.
I also suspect that this has the potential to make the area of toxic torts much more scientifically based.
I am also wondering whether you may be interested in writing an article for my journal, Dose Response, on what might be the many risk assessment implications of the present new action and what EPA hopes it will lead to. While it may be to far in the future, this would be an excellent area for a presentation at our annual Dose Response conference....next April 16/17, 2019....just missed 2018 which was last week!!!

Given our discussions last week, I strongly suspect it may be of value for us to continue our discussions. This may be especially in the areas of concepts such as additive to background, hormesis and emerging very serious weaknesses of the LNT and its very corrupt origins and integration within US regulatory agencies.
Let me know what you think.

Sincerely,

Ed

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 4/20/2018 1:01:07 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: see this attempt

The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses
In toxicology and epidemiology and the need to incorporate such data in the risk assessment process. Confidence in the continued use of the LNT model
as a default in cancer risk assessment has been seriously eroded by advances in modern molecular toxicology. These new findings strongly support this proposal
and its goal to place cancer risk assessment on an improved scientific foundation. Continuing reliance on the LNT the default in cancer risk is not scientifically defensible.

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 4/19/2018 10:46:41 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: follow up

Clint:

One important nuance in the risk assessment game that that to avoid LNT one needs to somehow avoid the built-in assumption of additive to background. This is why I included the term hormesis in my sentence. Even if additive to background is assumed the linearity estimate would not occur with the hormesis model but could with the threshold. Thus, this is a very important consideration. Thus, I believe that the sentence I added is necessary in the write up.

Ed

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 4/19/2018 9:19:54 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: FW:
Attachments: FoodChemTox-Horm-LNT.pdf

Clint:

One more try:

"EPA shall also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on the major competing models (LNT, Threshold and Hormesis)."

See the attached paper that described the concept and statement I provide here.

Ed

From: Edward Calabrese
Sent: Thursday, April 19, 2018 4:11 PM
To: 'Woods, Clint' <woods.clint@epa.gov>
Subject: FW:

Clint: See the slight rewording:

"EPA shall also incorporate the concept of model uncertainty to optimize low dose risk estimation based on the major competing models (LNT, Threshold and Hormesis)."

From: Edward Calabrese
Sent: Thursday, April 19, 2018 3:55 PM
To: 'Woods, Clint' <woods.clint@epa.gov>
Subject: RE:

Clint:

It is good what has been written but it needs a little more. I would strongly suggest that you add one more sentence to the end of the paragraph on page 12:

"EPA shall also incorporate the concept of model uncertainty for low dose risk estimation based on the major competing models (LNT, Threshold and Hormesis)."

This phase is important because at 10-4 cancer risk from LNT, the nadir of the hormesis curve and the traditional threshold risk assessment safe exposures converge.
This approach integrates the three models and comes up with a regulatory "sweet spot".
Thus, by combining the use of the three models in a type of model uncertainty mode one can in effect change the risk paradigm to something more scientifically justifiable, which protects the public from harm and creates the distinct

potential for profound public health benefit. I have published multiple papers on this topic along with the scientific justification.
Call me to discuss either at work or home.

Ed

From: Woods, Clint <woods.clint@epa.gov>
Sent: Thursday, April 19, 2018 9:51 AM
To: Edward Calabrese <edwardc@schoolph.umass.edu>
Subject:

Thanks!

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

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Review

Cancer risk assessment: Optimizing human health through linear dose–response models

Edward J. Calabrese [a,*], Dima Yazji Shamoun [b], Jaap C. Hanekamp [c]

[a] School of Public Health & Health Sciences, Department of Environmental Health Sciences, Morrill I N344, University of Massachusetts, Amherst, MA 01003, USA
[b] Mercatus Center, George Mason University, 3434 Washington Blvd., Arlington, VA 22201, USA
[c] Roosevelt Academy, Lange Noordstraat 1, NL-4331 CB Middelburg, The Netherlands

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ABSTRACT

This paper proposes that generic cancer risk assessments be based on the integration of the Linear Non-Threshold (LNT) and hormetic dose–responses since optimal hormetic beneficial responses are estimated to occur at the dose associated with a 10^{-4} risk level based on the use of a LNT model as applied to animal cancer studies. The adoption of the 10^{-4} risk estimate provides a theoretical and practical integration of two competing risk assessment models whose predictions cannot be validated in human population studies or with standard chronic animal bioassay data. This model-integration reveals both substantial protection of the population from cancer effects (i.e. functional utility of the LNT model) while offering the possibility of significant reductions in cancer incidence should the hormetic dose–response model predictions be correct. The dose yielding the 10^{-4} cancer risk therefore yields the optimized toxicologically based "regulatory sweet spot".

1. Introduction

The assessment of cancer risks from exposure to ionizing radiation and chemical carcinogens by regulatory agencies worldwide is typically performed via the use of linear at low dose modeling. The linear non-threshold (LNT) approach for cancer risk assessment was first proposed for cancer risk assessment by the U.S. National Committee for Radiation Protection and Measurement (NCRPM) in 1958, following the recommendation of the U.S. National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel to switch from a threshold to a linear model for assessing genomic risk from ionizing radiation in 1956 (Jolly, 2003; Whitemore, 1986).

The LNT approach was later adopted by regulatory agencies starting in the late 1970s assessing risks for chemical carcinogens in all media (e.g. air, water, food and soil) (National Academy of Sciences (NAS), 1977). The initial transition from the threshold to the LNT approach in the mid 1950s was made prior to the discovery of DNA repair, adaptive responses with chemical mutagens and ionizing radiation, apoptosis, pre-conditioning and the resurgence of the hormetic concept, all of which could affect the shape of the dose response in the low-dose zone. The clarification of different mechanisms of action for carcinogens has encouraged the development of cancer risk assessment methods that incorporate knowledge of species specificity and threshold. These approaches are often employed by the U.S. EPA and FDA and most European authorities for non-genotoxic carcinogens (Page et al., 1997; Whysner and Williams, 1992; Williams, 2001; Williams et al., 2012).

These developments have challenged the theoretical and mechanistic basis of the LNT, along with the recognition that epidemiological methods are in effect not capable of detecting risks below twice the normal background (Taubes, 1995). Furthermore, the massive mega-mouse study that used 24,000 animals was only able to estimate risk at the 1% level (ED01 study) (Bruce et al., 1981). Similar limitations were reported for a cancer bioassay study with >40,000 trout (Bailey et al., 2009). These methodological limitations along with the more recent developmental insights on the plethora of adaptive mechanisms that act at low doses have revealed limitations of the LNT model.

2. Developments

The dose–response model that has been shown to have biological plausibility, especially in the low dose zone, is hormesis, a biphasic dose–response. Current interest in hormesis can be traced back to the research of Thomas Luckey on radiation hormesis (Luckey, 1980) and on chemical hormesis by Tony Stebbing (Stebbing, 1982). These researchers stimulated the electric power utilities of Japan

* Corresponding author. School of Public Health & Health Sciences, Department of Environmental Health Sciences, Morrill I N344, University of Massachusetts, Amherst, MA 01003, USA. Tel: +1 413 545 3164; fax: +1 413 545 4692.
E-mail address: edwardc@schoolph.umass.edu (E.J. Calabrese).

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0278-6915/

and the U.S. to conduct the first hormesis conference in August, 1985. These three events reactivated interest in the hormesis concept.

Since the initial hormesis conference mentioned here, multiple books have been published on hormesis (Calabrese, 1992, 1994; Costantini, 2014; Elliott, 2008; Luckey, 1992; Mattson and Calabrese, 2010; Rattan and LeBourg, 2014; Sanders, 2010; Stebbing, 2011). Also, many chapters on hormesis in toxicology and pharmacology texts have been produced; hormesis has been the focus of more than a dozen conferences; multiple symposia at major society meetings have addressed hormesis. It is the subject of more than 2000 scientific publications in peer-reviewed journals, and the object of more than 30,000 citations in the Web of Science/Knowledge. Extensive documentations of hormetic dose responses have been summarized from a large and continuously updated database (Calabrese and Blain, 2005, 2009, 2011).

The hormetic dose–response was also found to make more accurate predictions than the LNT or threshold dose–response models in head-to-head comparisons using large, independent data sets (Calabrese and Baldwin, 2003; Calabrese et al., 2006, 2008). Detailed mechanisms of 400 hormetic dose responses have recently been summarized (Calabrese, 2013). Additionally, the hormetic dose response therefore has been demonstrated to be highly generalizable, being independent of biological model (i.e., phylogenetically diverse – from bacteria to humans; in vitro and in vivo), level of biological organization (i.e., cell, organ and organism), endpoint, inducing agent and mechanism.

3. Objective – Integration

Based on these features, it has been proposed that the hormetic dose–response should become the default model for risk assessment for both carcinogens and non-carcinogens. The hormesis database provides strong evidence that dose–response relationships for carcinogens (e.g., DDT, dioxin, multiple PAHs, ionizing radiation) and non-carcinogens typically display hormetic dose response patterns with similar quantitative features. While this line of argument has been made (Calabrese, 2004), this is not the purpose of this paper. The present paper proposes a "practical" and straightforward harmonization of both the LNT and hormetic models for cancer risk assessment. As is customary in such convergences, common ground is sought by various entities (e.g., regulatory agencies and regulated industries), while differences are still recognized and will remain unresolved for now.

We see the following reasons why integration of both models would be beneficial. First, if hormesis describes low-dose exposure impacts of chemicals/ionizing radiation more accurately than the LNT-model does, then the regulatory authorities should apply the best that the toxicological sciences have to offer. The hormetic dose response requires rigorous study designs in order to be properly evaluated, with large numbers of doses, with proper dose spacing, and often within a dose–time framework. When such data are available, the hormetic dose response has far outperformed the threshold and linearity dose response model for accuracy in estimating low dose effects (Calabrese and Baldwin, 2003; Calabrese et al., 2006, 2008).

Second, considering the developments in analytical chemistry, increasingly lower levels of chemicals can be detected. We have entered the realm of atto- (part per quintillion; 10^{-18}) and zeptomoles (part per sextillion; 10^{-21}) of detectable analytes (Pagnotti et al., 2011). Consequently, the unspoken 'logic' of the LNT-model infers that a 'clean bill of health' can never be truly given (Hanekamp et al., 2012). The technology-driven stringency of regulation in the context of the LNT-model can be attenuated with the aid of the biphasic dose–response model. As a result, regulatory expenditures will be reduced along with benefit optimization (Keeney, 1997).

Third, the biphasic dose–response model underscores the beneficial adaptability of organisms' responses to chemical exposure, whereby regulation that expresses the functional integration of both the LNT and hormetic models is better able to address society's fears of carcinogen exposure.

4. Integration – Roadmap

How then do we envision this integration, that is, the harmonization of the hormesis and LNT dose response models for cancer risk assessment? The reconciliation of these two divergent models can surprisingly be made in a direct and uncomplicated fashion.

1) The key aspect of the hormesis/LNT convergence is that when risks are based on chronic animal bioassay studies, the optimal protective effects (i.e., reduction in tumor incidence for the affected below the control group) is predicted to occur at the same dose at which the LNT predicts 10^{-4} risk.
2) To achieve this value, the hormetic-based approach would first estimate a 1% response from the animal bioassay via a BMD-type methodology. When this derived-dose is divided by factor of 100, it yields slightly less than a risk of 10^{-4}. This was shown to be the case for ten highly diverse data sets by Gaylor (1989). The hormetic risk assessment methodology of Calabrese and Cook (2005), which is optimized at the same dose that the LNT estimates a 10^{-4} risk level, predicts benefit while the LNT estimates enhanced cancer risk.
3) We propose that cancer risk assessment adopt an acceptable risk of 10^{-4} using the LNT model since this dose would also yield the optimal hormesis dose response benefit. This dose is the so-called regulatory "sweet-spot" that provides substantial protection against theoretical low dose risks that are far below the detection of even the most demanding epidemiological and toxicological studies/methods, while including benefits predicted by the hormetic dose response model (Fig. 1). This approach would also have the significant societal benefit of affecting a profound reduction in costs (i.e., financial and predicted adverse health), markedly affecting cost/benefit analyses.
4) In a population of one million people, the 10^{-4} risk predicts 100 people (i.e., 10^6 people $\times$ 10^{-4} risk = 100) affected with an organ-specific cancer (e.g., lung, kidney, bladder, etc.) by some deleterious agent that is added to the background for cancer of that organ (Fig. 1). Assuming a 25% tumor background

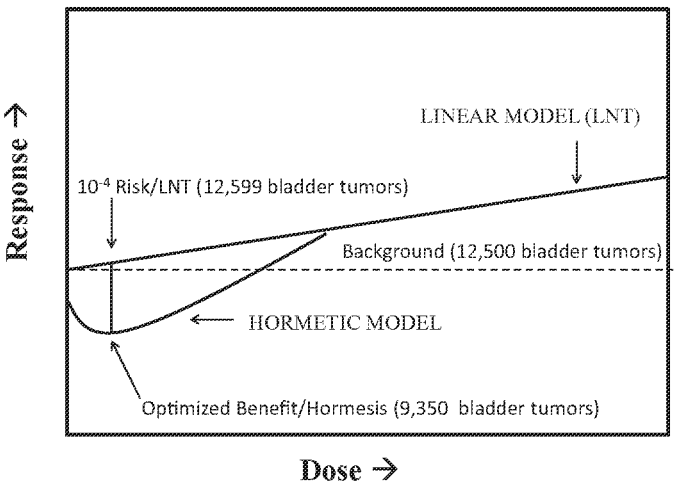

Fig. 1. Functional integration of hormesis and LNT for carcinogen risk assessment; derivation of the optimal regulatory strategy.

incidence, 250,000 of the one million people would be predicted to develop tumors. If the organ in question was responsible for 5% (e.g., bladder) of the above 25% (i.e., 250,000 people), it would represent 12,500 of the 250,000 people with cancer (i.e., $0.25 \times 0.05 = 0.0125$) ($0.0125 \times 10^6 = 12{,}500$). Many organ-specific tumors, including the bladder, affect about 3.5 to 6.0% of the tumor occurrence (National Cancer Institute (NCI), 2014), thus the use of 5% for an organ like the bladder would be a reasonable expectation. Organs affecting a notably higher proportion of people (e.g., about 16–18% per cancer type) are those cancers of the lung, breast and prostate. The 100 newly affected people with *chemically* induced bladder cancer are then randomly distributed among the entire population of one million. This suggests that 25% of the 100 will already be in the process of developing a background tumor, with about 5% of those already targeted for a "spontaneous" bladder tumor ($0.25 \times 0.05 = 1.25\%$). The net result of background (i.e. spontaneous) and tumor-induction via a chemical carcinogen at 10^{-4} is 12,500 ("background") plus 100 new chemically induced cases (i.e., $12{,}500 + 100 = 12{,}600$) minus 1 due to spontaneous and induced bladder tumors in the same individuals. This would yield a total of 12,599 individuals with bladder cancer. The hormetic benefit is likely to affect both background and induced tumor incidence, reducing their incidence by roughly 25% (Calabrese and Blain, 2011), lowering the predicted total number of affected people (12,500) by about 3150. There can be other situations in which the chemical may affect multiple organs with different tumor backgrounds and induced tumor incidence, affecting the nature and complexity of the assessment. For example, in the case of dioxin, it was shown in the Kociba et al. study (Kociba et al., 1978) that has been widely used for cancer risk assessment that hormetic effects appear to occur in multiple organs (i.e., Females: liver, ovary, uterus, cervix/vagina, mammary, pituitary and adrenal; Males: liver, pulmonary, pituitary, pancreas and adrenal). In such cases it may be possible to select that dose which displays the lowest overall tumor incidence for risk assessment purposes. In theory, this type of situation may be predicted to have a greater beneficial effect than described for the bladder cancer. However, it would not be unexpected for the optimal effect to vary by organ. Using a financial metaphor, the convergence of the LNT/10^{-4} risk and hormesis methodologies permits the protection of one's "principle" (i.e., impossible to detect chemically-induced increase in cancer risk) while adding considerable benefit (i.e., large reduction in cancer risk for those affected organs). This compromise strikes an optimized balance in which there is a very low theoretical risk increase and a very high theoretical benefit. Choosing a 10^{-6} acceptable risk would reduce 99 of the 100 theoretically affected people while eliminating the possible hormetic benefit. This type of strategy would prevent the possibility of beneficial effects, which could be substantial.

5) The example presented above addresses the risk of a single complete carcinogen. However, humans live in a highly complex environment involving exposure to a vast array of complete carcinogens, tumor promoters, chemoprotective chemicals and physical agents, all superimposed on dynamic metabolic processes, numerous adaptive mechanisms and complex exposure dynamics. Predicting cancer incidence of complex mixtures from experimental and epidemiological studies is problematic, if not impossible. A very limited, simplified and yet mechanistically oriented approach to assess complex carcinogenic mixtures is the toxic equivalent factor (TEF) that assumes additive processes that act identically (e.g. same receptor) for similarly grouped agents (e.g. dioxins, PAHs and PCBs). The TEF concept was integrated within a LNT perspective. Epidemiological evaluations of complex mixtures reveal the failure of predictions of animal studies to predict human responses. For example, a cup of coffee contains >1000 chemicals of which approximately 30 have been tested for cancer. Of these the majority were carcinogenic in standard rodent model testing. Each cup of coffee contains >10 mg of rodent carcinogens, with American adults drinking three cups per day (Ames and Gold, 2000; Gold et al., 1992). The situation gets more complex as more carcinogens are added via the roasting process. However, despite such exposures to natural and roasted process-related carcinogens, comprehensive epidemiological studies reveal neutral or beneficial effects from lifetime coffee drinking depending on the organ (Bohn et al., 2014; Crippa et al., 2014). Thirty-two occupational epidemiological studies (i.e. case–control – 19 studies; cohort – 13 studies) of gasoline exposure which is a highly complex and variable mixture of >500 saturated/unsaturated hydrocarbons revealed no pattern or clear association between gasoline and any cancer (Keenan et al., 2010). Furthermore, dose responses of complex mixtures [e.g. petroleum (Laughlin et al., 1981), waste-water treatment effluents (De Nicola et al., 2004; Mendoza-Figueroa, 1973; Walsh et al., 1982), complex organochlorine mixtures (Aube et al., 2011)] over a broad dose response often conform to an hormetic dose response. These findings support the conclusion that complex mixtures can induce hormetic dose responses and can be evaluated within the framework proposed here.

6) An important implication of model uncertainty is that it has the potential to undermine and challenge the use of LNT in toxic tort litigation cases. The acknowledgement of substantial and unresolved uncertainty in risk assessment may preclude causation judgments with low dose exposures. In fact, the use of LNT in toxic tort cases in the United States has been successfully challenged in numerous litigations affecting ionizing radiation, asbestos as well as chemical carcinogens, principally due to its lack of validation capacity, inconsistency with published findings and the recognition of substantial adaptive mechanisms that undermine an LNT interpretation (Milward v. Acuity Specialty Products Groups, Inc, 2013; Sutera v. Perrier Group of America Inc, 1997; Whiting v. Boston Edison Co, 1995).

5. Discussion

The search for public health common ground via the integration of opposing risk assessment models is a new approach in the process of risk assessment harmonization. It permits the strengths of opposing perspectives to be incorporated into a unified risk assessment approach. It is recognized that estimates of low risk is a speculative activity, especially when the data are derived from high dose toxicology studies and that there is no current practical way around this limitation. The present recommendation is viewed as substantially conservative, creating the opportunity to benefit from the induction of adaptive responses while recognizing and incorporating model uncertainty into the risk assessment process. We believe that this is a sound foundation upon which to base environmental public health policy.

The precautionary principle, which is at the core of modern governmental environmental health policies, is founded on a toxicological assumption that lower is always safer/better and that zero exposure, especially for carcinogens, is the goal [maximum contaminant level goal (MCLg)] as seen for EPA drinking water standards. The precautionary principle was strongly influenced during its formative development by belief in LNT predictions. Harmonizing of the LNT and hormesis dose response models can provide a vehicle not only for cancer risk assessment but also a novel means, along

with a more biologically based foundation, to guide a broad range of precautionary principle applications.

Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

Acknowledgement

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Message

From: Millett, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=C067CAA6C93544F78C26AB08CC567D27-MILLETT, JOHN]
Sent: 10/3/2018 1:29:37 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: Fwd: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

FYI

Sent from my iPhone

Begin forwarded message:

From: "Veal, Lee" <Veal.Lee@epa.gov>
Date: October 2, 2018 at 3:09:52 PM EDT
To: "Millett, John" <Millett.John@epa.gov>, "Wieder, Jessica" <Wieder.Jessica@epa.gov>
Subject: FW: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

FYI

Lee Ann B. Veal
Director, Radiation Protection Division
Office of Radiation and Indoor Air
Office: 202-343-9448; Cell: 202-617-4322
www.epa.gov/radiation

From: Konkus, John
Sent: Tuesday, October 02, 2018 2:04 PM
To: Knickmeyer, Ellen <EKnickmeyer@ap.org>
Cc: Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
Subject: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards
Importance: High

Ellen: Your article frames this issue as a "radiation regulation" but we told you in our statement (see below) that this proposed rule "did not discuss radiation." There is no "radiation regulation" as you put it. Please retract your article before other outlets follow this mistake.

Also the strengthening transparency in science comment period has already closed.

From: Konkus, John
Sent: Friday, September 14, 2018 10:53 AM
To: 'Knickmeyer, Ellen' <EKnickmeyer@ap.org>
Cc: Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
Subject: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

The Radiation Health Effects site reflects recent information and was last updated in July 2018.

EPA's proposed rule on Strengthening Transparency in Regulatory Science did not discuss radiation. The Agency did seek comment on increasing transparency of the assumptions underlying dose response models. As noted previously, the timeline for any future action on this proposal has not yet been determined and EPA is reviewing more than 500,000 comments.

EPA continues to use the linear-no-threshold model for population-level radiation protection purposes. The EPA's Radiation Protection Program acknowledges uncertainty regarding health effects at low doses and is supportive of continued research in this area. More information in support of this approach can be found in the International Commission on Radiological Protection Report 103 and the 2018 National Council on Radiation Protection and Measurements Commentary 27.

From: Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
Sent: Friday, September 14, 2018 8:34 AM
To: Konkus, John <konkus.john@epa.gov>
Cc: Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
Subject: Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thank you.

Sent from my iPhone

On Sep 14, 2018, at 8:30 AM, Konkus, John <konkus.john@epa.gov> wrote:

> Ellen: We're working on something more robust for you. Should have it this morning.
>
> John
>
> Sent from my iPhone
>
> On Sep 14, 2018, at 5:52 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
> > Hi, Enesta,
> >
> > That EPA website entry you sent me a link to seems to be a contradictory statements saying exposures below 10 rem usually have no harmful health effects but the EPA still follows the guideline that no exposure is safe.
> >
> > When does that entry date from? When was it revised and what part was revised?
> >
> > Your other statement provides no information at all, except to indicate the EPA may decide to reverse its longstanding policy on radlation exposure without any advance notice to the public it is considering doing that.
> >
> > Can you answer my questions and provide an EPA expert to speak to?

These are non-answers and public silence on important public health questions for Americans.

Best,
Ellen

Sent from my iPhone

On Sep 13, 2018, at 6:01 PM, Jones, Enesta <Jones.Enesta@epa.gov> wrote:

> Ellen,
> I inadvertently cut off the end of our response. Here it is:
>
> Find more information here: https://www.epa.gov/radiation/radiation-health-effects
>
> Ellen,
>
> "EPA is currently reviewing the more than 590,000 comments on the Strengthening Transparency in Regulatory Sciences proposal. The EPA will determine a timeline for a decision after it has more fully assessed the comments." — **EPA spokesperson**
>
> On Sep 13, 2018, at 10:32 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
> Hello – wanted to also ask, is this still EPA policy?
> https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
> "Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."
>
> "Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."
>
> Best,
> Ellen

From: Knickmeyer, Ellen
Sent: Thursday, September 13, 2018 10:06 AM
To: 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>
Cc: 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
Subject: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts: "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
202 641 9487
415 699 0865
eknickmeyer@ap.org
ellen.knickmeyer@gmail.com

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Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 4/24/2018 2:58:45 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: RE: follow up

Clint:

Congratulations!!! This activity is critical... I am good with the quote and hope it helps.
I suspect I will not be a hero on my campus....but I know we are on the correct scientific path.

Ed

From: Woods, Clint <woods.clint@epa.gov>
Sent: Tuesday, April 24, 2018 10:53 AM
To: Edward Calabrese <edwardc@schoolph.umass.edu>
Subject: RE: follow up

Dr. Calabrese,

Hoping to have announcement later today – May be some minor changes in the proposal as a result of White House feedback. If you're OK, here's a statement for you as edited for brevity by our press team:

"The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process," **said Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts**

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

From: Edward Calabrese [mailto:edwardc@schoolph.umass.edu]
Sent: Monday, April 23, 2018 8:16 PM
To: Woods, Clint <woods.clint@epa.gov>
Subject: follow up

Clint:

Is it still looking good for the EPA proposal we have worked on to go forward in the process this week?

Ed

Message

From: POLITICO Pro Energy [politicoemail@politicopro.com]
Sent: 10/3/2018 9:54:45 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: Morning Energy, presented by Growth Energy: Mountain Valley Pipeline stumbles again — PJM's new proposal for FERC — NOPEC's moment?

By Annie Snider | 10/03/2018 05:52 AM EDT

With help from Ben Lefebvre, Alex Guillen and Darius Dixon.

PROGRAMMING NOTE: Morning Energy will not publish on Monday Oct. 8. Our next Morning Energy newsletter will publish on Tues. Oct. 9. Please continue to follow Pro Energy issues here.

MORE LEGAL TROUBLE FOR MOUNTAIN VALLEY PIPELINE: The 4th Circuit U.S. Court of Appeals dealt a major blow to the West Virginia pipeline project Tuesday when it vacated its Army Corps of Engineers permit, finding that the project didn't meet the requirements for a nationwide permit to harm streams and wetlands. The court vacated that verification and said it would explain its reasoning more fully in a forthcoming opinion, Pro's Ben Lefebvre reports.

Sierra Club Executive Director Michael Brune called on FERC to halt construction of the pipeline in light of the court's decision. "In their haste to make a quick buck, MVP rushed essential processes because they knew there was no way their dirty project would ever satisfy commonsense protections for water and health," he said in a statement.

"Disappointed" but not defeated: The project's developer, Mountain Valley Pipeline LLC said in a statement that it is assessing whether it can continue construction in areas that don't impact streams and wetlands along the 160 miles of the route covered by the vacated permit, and that it plans to apply for a new Army Corps permit following changes to permit when West Virginia's state certification process. The company said it expects to secure a new permit in early 2019 and hopes to have the pipeline fully in service by the fourth quarter of 2019.

PJM OFFERS NEW PITCH TO SATISFY FERC: Tuesday was the deadline to submit the initial round of comments to FERC's contentious order requiring that the nation's largest power market, PJM Interconnection, rewrite its capacity market rules to account for state-level policies like nuclear or renewable subsidies. Nobody expected PJM's response to be simple, but the proposal adds even more layers to the already complex capacity market, which effectively pays power plant owners to be available when the grid needs them most. In addition to setting up a price floor for generators to bid in, PJM suggests creating a "resource carve-out" mechanism, which would let states support a subsidized plant but remove them from the capacity auctions, as well as an "extended resource carve-out" for FERC to consider if they don't think that goes far enough.

PJM gave everyone a lot to chew on so you'll have to make the most of the time you have between now and Nov. 6 to tell FERC what you think.

A little help on the way? A couple of ME tipsters tell us that the White House is primed to announce its next pick for the FERC leadership, Bernie McNamee, as soon as this week.

WELCOME TO WEDNESDAY! I'm your guest host, Annie Snider, and am eternally grateful for all the bagel suggestions. The ME hivemind has spoken and Bullfrog is clearly the place to service our NYC bagel

needs (the whitefish salad, and jalapeno cream cheese were specifically endorsed). We'll see about that! But ME would be remiss if we didn't mention some honorable mentions: So's Your Mom, and Buffalo and Bergen.

Today's trivia question: Name the scientist who coined the phrase "global warming." Ben takes the reins to carry us until Kelsey's much-awaited return, so send your guesses, along with your tips, energy gossip and comments, to blefebvre@politico.com, and remember to follow us on Twitter @Morning_Energy and @POLITICOPro.

PRESIDENT DONALD TRUMP SAYS A RED WAVE IS COMING ON ELECTION DAY. Is he right, or will the tide turn blue? Compete against the nation's top political minds in the POLITICO Playbook Election Challenge, by correctly picking the winning candidates in some of the most competitive House, Senate and gubernatorial races in the country. Win awesome prizes and eternal bragging rights. Sign up today! Visit politico.com/playbookelectionchallenge to play.

NOPEC GAINING? Gas prices are rising, and so is animosity toward OPEC. The oil cartel, which President Donald Trump bashed at the United Nations last week, may find itself in the crosshairs again today at a Senate Judiciary subcommittee hearing on antitrust laws. The hearing will not focus explicitly on the Judiciary Chairman Chuck Grassley's NOPEC bill, S. 3214 (115) (115), which would allow the attorney general to bring antitrust lawsuits against OPEC members in U.S. courts. Sen. Mike Lee, who chairs the antitrust subcommittee holding today's hearing, is a co-sponsor of the bill, as is subcommittee ranking member Amy Klobuchar. Today's hearing may offer members of the Trump administration a chance to weigh in on the bill, and committee aides tell ME they expect it will "probably" come up.

Versions of NOPEC have floated around for years without becoming law, but supporters may now have an ally in the president, who has complained on Twitter about OPEC for years. Just last week, Trump accused OPEC of "giving us high oil prices," in his speech to the U.N. general assembly. "OPEC is a pet peeve for him," Joe McMonigle, a senior energy policy analyst at Hedgeye Potomac Research told Reuters. "Everybody thinks he could easily support NOPEC." The average U.S. gasoline price reached $2.90 a gallon this week, up about 40 cents from a year ago, according to price tracking website Gasbuddy.com.

Assistant Attorney General Makan Delrahim, of the Justice Department's Antitrust Division, will be among today's witnesses; in 2008, while working in private practice, he endorsed an earlier version of the NOPEC bill. Grassley and House Judiciary Committee Chairmen Bob Goodlatte wrote to Delrahim in August asking for his input on this year's bill, and the committee said Tuesday it never received a reply.

And what if it becomes law? The U.S. could challenge Saudi Arabia and other cartel members under anti-trust laws if the NOPEC bill were ever enacted, but it's not necessarily clear to ME what could be won. Some analysts fear any lawsuit would simply provoke backlash from the cartel. "I have seen this type of proposal in the past, especially when prices rise," said Andy Lipow, president of Lipow Oil Associates, told ME. "The fear might be that if the U.S.A. litigated or seized assets, OPEC would simply take more oil off the market, sending prices higher. In the worst case, they stop selling to the U.S.A."

COMPLEX OZONE LAWSUIT GOES TO COURT: The D.C. Circuit Court of Appeals hears oral arguments today over a 2016 rule incorporating the 2015 ozone standard into the Cross-State Air Pollution Rule, which seeks to curb pollution from upwind states. Many of the issues are highly technical, and have to do with how pollution is measured, patterns are modeled, or emissions allowances were allocated. But the rule is under attack from two sides. Environmental and public health groups say the rule wasn't stringent enough, while industry and state challengers say it went too far. The case will be heard by Judges Sri Srinivasan, Patricia Millett and Robert Wilkins, all Barack Obama appointees.

One big reason the Trump administration is defending this Obama rule: EPA has relied on this ozone update to justify recent decisions not to require upwind states to cut even more emissions. In July, EPA said it

believes upwind states have done enough because of this regulation, and thus do not need to find further ways to curb pollution. And last month EPA rejected petitions from Maryland and Delaware asking it to require upwind states to do more about their pollution, saying those smokestacks are already covered under the 2016 update.

If you go: 9:30 a.m. at the E. Barrett Prettyman Courthouse; the hearing will also be audiostreamed on the court's website.

MURKOWSKI, BISHOP HUDDLING ON LWCF: Senate Energy Chairman Lisa Murkowski (R-Alaska) has held some initial conversations with House Natural Resources Chairman Rob Bishop (R-Utah) about a possible path forward on reauthorizing the Land and Water Conservation Fund, she told reporters Tuesday. Both Murkowski and Bishop have raised concerns about the mandatory funding included in the measure to permanently reauthorize the LWCF, S. 569 (115), which was advanced by Senate Energy earlier Tuesday. "I want this measure to pass," Murkowski told reporters. "Working with our colleagues in the other body is going to be important as we advance what I think we all agree is a national priority — and it should be a national priority. We'll figure it out." More from Anthony Adragna here.

IT'S STILL GOOD, IT'S STILL GOOD: Alaska Gasline Development Corp. — the company behind the state's proposed Alaska LNG export terminal and pipeline — wants everyone to know that there's still room for its project after Shell announced yesterday it would build its own LNG terminal in British Columbia. Shell's LNG Canada, with a planned capacity of up to 14 million metric tons a year to be built by the middle of next decade, would target buyers in Asia, the same market the Alaska Gasline project is shooting for. In response, Alaska Development said it "reaffirmed" its agreement it signed last year with Chinese chemical company Sinopec, the Bank of China and China Investment Corp. to pursue an LNG project. "The supplemental agreement reaffirms the parties' intent to negotiate and conclude definitive agreements by December 31, 2018," Alaska Development said in a prepared statement.

APPEALS COURT OPENS DOOR TO PFAS LITIGATION: Residents whose drinking water has been contaminated by the military's use of firefighting foam can sue for government-funded medical monitoring, the U.S. Court of Appeals for the 3rd Circuit ruled Tuesday, poking a hole in the government's immunity defense. The joined cases were brought by two families in eastern Pennsylvania who say their drinking water wells were contaminated with the chemicals at levels far above EPA's health advisory level. A federal district court had dismissed the cases as barred under the Superfund law, but on appeal the 3rd Circuit held that the families could proceed with a portion of their case and seek medical monitoring.

SEE YA IN SEATTLE: Acting EPA Administrator Andrew Wheeler is in Seattle today , and will tour construction of the first major water infrastructure project to receive funding under the WIFIA loan program. The EPA in April approved up to $134.5 million in loans for the Georgetown Wet Weather Treatment Station in Washington state's King County. The project is designed to collect and treat up to 70 million gallons of wastewater and stormwater each day that would otherwise spill into the Duwamish River, and ultimately Puget Sound, during heavy storms. On Thursday, Wheeler will hold a press conference at EPA's Region 10 office.

SECRET SCIENCE ON THE HILL: A Senate Environment and Public Works subpanel takes up the topic of scientific transparency today, as EPA considers how to finalize the controversial rule it proposed this spring that would block the agency from using many studies looking at the effects of pollution on human health.

One of the less discussed aspects of the EPA proposal may also get some airtime — the move to change the default assumption that there is no safe level of exposure for carcinogens, which has been the focus of a major battle between the chemicals industry and public health advocates for years. Witness Edward Calabrese, a

toxicologist at the University of Massachusetts, Amherst, hailed the change as "correct and long overdue" in comments on the rule, while advocates have argued it runs counter to increasing scientific evidence that there is no "safe threshold" of exposure to toxic chemicals.

Implications for radiation? The Associated Press reported Tuesday that those changes could affect how the federal government regulates radiation exposure for everything from workers at nuclear facilities to people living next to Superfund sites to medical workers doing X-rays and CT scans. Calabrese "has said weakening limits on radiation exposure would save billions of dollars and have a positive impact on human health," the AP reports.

If you go: The hearing is at 2:15 p.m. in Dirksen 406.

ON ONE HAND: Ardent Trump supporter Rep. Steve King (R-Iowa) tweeted a picture of his agenda — including E15 — written on his hand for what he said was a 75-minute private meeting with President Donald Trump.

GET 'EM OUTTA HERE: The Army Corps of Engineers, one of the country's main dam builders, took a major step to incentivize the removal of obsolete dams Tuesday, issuing guidance to its district offices on how to count the environmental benefits of removing dams when issuing mitigation credits. Developers spend billions of dollars each year on mitigation required by the Army Corps to offset damage to streams and wetlands. Those credits can be earned by restoring or creating wetlands and streams, but that has rarely included removing dams, which the Corps said in a statement are often more than a century old and create not just environmental harm but also public safety hazards.

LAME-DUCK FUNDING FIGHT LOOMS: When the House returns after the Nov. 6 elections, Speaker Paul Ryan and his deputies will have just four weeks to pass funding bills that keep the federal government open through the holidays — and the way they played the last funding fight this fall stands to make their job that much harder, Budget & Approps' Sarah Ferris reports this morning.

Leaders gave up their best leverage for enticing votes from both sides of the aisle by already approving an entire year of military funding and the vast majority of the government's non-defense spending. Without that to use as a bargaining chip, House GOP negotiators will be expected to deliver far more Republican policy victories to gain the votes from their own party. And if Democrats take the House, partisan battle lines are likely to harden on everything from President Donald Trump's demand for a border wall to environmental policies at the Interior Department. Read the full story here.

MORE CRES ENDORSEMENTS: The GOP clean energy group Citizens for Responsible Energy Solutions will make its third round of congressional endorsements this morning. Republicans winning the group's backing are Reps. Don Bacon (Neb.), Mike Coffman (Colo.), John J. Faso (N.Y.), Chuck Fleischmann (Tenn.), Garret Graves (La.), John Katko (N.Y.), Adam Kinzinger (Ill.), Leonard Lance (N.J.), Markwayne Mullin (Okla.), Francis Rooney (Fla.), Mimi Walters (Calif.), Kevin Yoder (Kan.), Ted Yoho (Fla.) and Lee Zeldin (Fla.), as well as Dusty Johnson, a candidate for South Dakota's House seat.

CAP ON TONGASS: Ahead of today's public hearing on whether to exempt the nation's largest national forest from federal rules limiting construction in national forests, the Center for American Progress has a report arguing that timber production in the Tongass national forest is a waste of taxpayer dollars and harms other industries, including fisheries and tourism.

QUICK HITS

— "Trump's Import Tariffs Will Make U.S. Wind Power More Expensive." Bloomberg

— "PJM: FirstEnergy can shut 4 GW of fossil plants without harming reliability." UtilityDive

— "Elon Musk's Ultimatum to Tesla: Fight the SEC or I quit." New York Times

— "In about-face, Gov. Bruce Rauner calls for Sterigenics shutdown after weeks of downplaying cancer risks." Chicago Tribune

HAPPENING TODAY

9:30 a.m. — Natural Gas Supply Association winter outlook briefing. Bloomberg Room at the National Press Club Press, 529 14th Street N.W.

1:30 p.m. — U.S. Forest Service public hearing on exempting the Tongass National Forest from the federal Roadless. Holiday Inn Capitol, 550 C Street S.W.

2:15 p.m. — Senate Environment and Public Works subcommittee on Superfund, Waste Management, and Regulatory Oversight hearing titled "EPA Oversight of the Environmental Protection Agency's Implementation of Sound and Transparent Science in Regulation." 406 Dirksen.

CORRECTION: The Oct. 2 edition of Morning Energy misidentified the organization that helps energy companies address methane leaks. It is the Oil and Gas Climate Initiative.

That's all for ME!

To view online:
https://subscriber.politicopro.com/newsletters/morning-energy/2018/10/mountain-valley-pipeline-stumbles-again-360685

Stories from POLITICO Pro

Court delivers new setback for Mountain Valley pipeline Back

By Ben Lefebvre | 10/02/2018 07:28 PM EDT

A U.S. appeals court vacated an Army Corps of Engineers permit for the Mountain Valley Pipeline in West Virginia today, a potentially major setback for the developer of the proposed natural gas conduit.

The order from the 4th Circuit U.S. Court of Appeals in West Virginia said the Corps improperly verified the pipeline complied with a nationwide permit. The court vacated that verification and said it would explain its reasoning more fully in a forthcoming opinion.

The ruling may hinder Mountain Valley's ability to continue construction of the pipeline in what has already been a litigious, on-again-off-again project. Mountain Valley Pipeline LLC said in late September that court-

ordered work stoppages along the route caused it to bump the project's total cost estimate to $4.6 billion. A company spokesperson did not immediately reply to questions.

"Because the court has vacated the [permit] in its entirety, we anticipate that FERC is likely to issue a broad stop work order, halting construction on all incomplete water crossings (unless there are strong environmental reasons not to do so)," ClearView Energy partners wrote in a note to clients.

The Sierra Club and other environmental groups that opposed the pipeline cheered the court's decision.

"In their haste to make a quick buck, MVP rushed essential processes because they knew there was no way their dirty project would ever satisfy commonsense protections for water and health," said Sierra Club Executive Director Michael Brune in a statement. "Now, FERC must require MVP to immediately stop construction on the pipeline."

To view online click here.

Back

Sources: DOE's McNamee to get FERC nod Back

By Eric Wolff and Darius Dixon | 08/08/2018 04:07 PM EDT

The White House plans to nominate Energy Department official Bernard McNamee to fill the FERC leadership seat being vacated by departing Commissioner Rob Powelson, three sources familiar with discussions tell POLITICO.

McNamee helped roll out Energy Secretary Rick Perry's proposal last year to save struggling coal and nuclear power plants — an issue that sources have said served as a key litmus test for Trump administration officials evaluating a replacement for Powelson, who is set to resign Friday.

FERC in January unanimously voted down that plan, which sought to create special payments for power plants capable of holding 90 days of fuel on-site. But the administration has been considering additional options such as invoking rarely used emergency powers to force power plants to run, which would potentially give McNamee a chance to provide the pivotal vote on the subsequent rates and rules as a commissioner.

It is unclear when President Donald Trump would formally nominate McNamee, and the vetting process still seems to be underway. It would likely take the Senate several months to confirm him, a process that would start with hearings at the Energy and Natural Resources Committee.

Neither the White House nor DOE immediately responded to requests for comment Wednesday.

McNamee, who runs the DOE's Office of Policy, has been in and out of the agency under Trump. He was deputy general counsel for energy policy last year when he worked on Perry's ill-fated proposal to FERC. In February, he left DOE for a senior post with the Texas Public Policy Foundation, a conservative think tank with ties to Perry, before returning to DOE in May.

Before joining the Trump administration, McNamee previously worked at McGuireWoods, as chief of staff to Texas Attorney General Ken Paxton and as an aide to Sen. Ted Cruz (R-Texas).

To view online click here.

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Murkowski says she's spoken with Bishop on LWCF Back

By Anthony Adragna | 10/02/2018 03:28 PM EDT

Senate Energy Chairman Lisa Murkowski (R-Alaska) said today she's held some initial conversations with House Natural Resources Chairman Rob Bishop (R-Utah) about a possible path forward to reauthorizing the Land and Water Conservation Fund.

"I want this measure to pass," she told reporters. "Working with our colleagues in the other body is going to be important as we advance what I think we all agree is a national priority — and it should be a national priority. We'll figure it out."

The Energy and Natural Resources Committee earlier today advanced legislation, S. 569 (115), permanently reauthorizing LWCF and providing mandatory funding despite Murkowski's serious concerns with that approach. Bishop has warned that mandatory spending would likely doom the Senate bill in the House, and he moved his own bill, H.R. 502 (115), without it in September.

"My concern is we won't be successful with this measure if we can't address that part," Murkowski said, adding that an offset would be required under Congressional Budget Office rules.

"Some may say that's just moving money from one pot to another," she said. "Yes, that is true, but when you talk about how items score around here, that is a reality."

To view online click here.

Back

Lame-duck funding woes await House GOP leaders Back

By Sarah Ferris | 10/03/2018 05:00 AM EDT

Republican leaders dodged an October shutdown. But the way they played that first round of funding could make it hard to finish the job come December — especially if the midterms don't sway in their favor.

When the House returns after the Nov. 6 elections, Speaker Paul Ryan and his deputies will have just four weeks to pass funding bills to keep the government fully functioning through the holidays.

Complicating that task is the fact that they have given up their best leverage to entice votes from both sides of the aisle by clearing the deck for an entire year on military funding and the vast majority of the government's non-defense spending.

Add to that a midterm outcome that flips the House to a Democratic majority and it could be nearly impossible to muscle through the seven outstanding bills for fiscal 2019, at best prompting another stint of stopgaps and at worst stoking a pre-Christmas shutdown with Republicans in charge.

"That's the danger in not getting more bills done," said Rep. Tom Cole (R-Okla.), a senior appropriator, before House lawmakers departed. "Maybe we can get it done, but the election will impact what happens."

With five weeks until polls close, budget observers are eyeing a handful of factors that will determine the fate of funding for those agencies:

Democrats take the House:

If the GOP is forced to surrender its eight-year House majority, partisan battle lines are likely to harden ahead of the Dec. 7 deadline for funding the many departments left hanging while others received full-year spending levels last month. That could heighten already well-trodden disputes on everything from President Donald Trump's demand for a border wall to environmental policies at the Interior Department and abortion restrictions for foreign aid.

A House that's even more polarized would make it far more difficult for leaders of both parties to strike a final funding deal, marking an abrupt end to Congress' most productive appropriations cycle in two decades and ensuring more spending uncertainty for the departments of Homeland Security, Commerce, Transportation, Housing and Urban Development, Justice, State, Agriculture and Interior, as well as foreign operations, the IRS, science programs and the EPA.

Last-minute GOP demands:

Unlike this summer, Republican leaders can't dangle funding for the Pentagon or the Department of Veterans Affairs to get their fellow conservatives on board with bipartisan funding bills, since they already spent that bargaining chip for fiscal 2019. So House GOP negotiators will now be expected to deliver more Republican policy victories, or risk falling short on votes from their own party, according to multiple lawmakers and aides.

"A lot of us who are defense and fiscal hawks are really getting put in some tough situations right now. It's frustrating, and I don't like it," Rep. Mark Walker (R-N.C.), chairman of the roughly 170-member Republican Study Committee, told POLITICO last week. He added that he'll have "some issues" to raise in any lame-duck spending package.

Roughly a half-dozen House Freedom Caucus members also suggested last week that they plan to stir up an immigration fight when Congress takes on funding for the Department of Homeland Security.

"We should be doing what we said," Rep. Jim Jordan (R-Ohio) said in a last-minute push for border wall funding, one day before the House passed the main fiscal 2019 spending package, H.R. 5895 (115). "That's the single biggest issue voters voted us into power to accomplish, and we haven't yet done that."

Appetite for shutdown:

Because Trump has already signed spending bundles that make up about 75 percent of all federal funding for the current fiscal year, hard-line Republicans could be more inclined to force a partial government shutdown, since it wouldn't hurt the VA or the military.

Whether the president would be willing to shut down the government over demands for more money to fund a wall along the U.S.-Mexico border is still an open question, though. Trump said this week that he has "a big decision to make after the election as to whether or not we go for it."

Dragging out the deadline:

Given early conservative backlash against the remaining spending bills, Republican leaders will almost certainly require help from Democrats to pass bipartisan measures on the floor.

GOP leaders could have trouble enticing that support, however, if Democrats are newly empowered by election results and insist on punting all funding decisions until they have ushered in a new majority in January.

"Their temptation might be to hold off until the new majority shows up. I advise them to not do that," Cole said. "We did that, waiting for the president. It doesn't get you anything more and just creates a lot of work and anger."

Another omnibus:

When the House adjourned last month, spending leaders were still negotiating an unfinished "minibus," H.R. 6147 (115), that includes funding for the departments of Agriculture, Interior, Transportation, and Housing and Urban Development, plus the IRS and EPA.

Conference negotiators could easily abandon work on that spending package now and simply wrap it up into a catchall omnibus with the remaining three fiscal 2019 bills that fund the departments of Homeland Security, Justice, State and Commerce.

"I don't think there is as much incentive," one House GOP aide said on the possibility of continuing talks on that four-bill package through November.

GOP appropriators like Sen. Richard Shelby (R-Ala.) have pushed to keep the "minibus" negotiations open through the fall, insisting that lawmakers are "very close" to a deal. But even Shelby acknowledged there is little chance of anything more than "some talk" getting done while House lawmakers are back home campaigning.

Lawmakers and aides have said that package has been repeatedly held up by policy issues within the Financial Services bill, while the other three measures — Transportation-HUD, Agriculture and Interior-Environment — are largely negotiated.

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Back

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 4/30/2018 11:23:40 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: LNT obit
Attachments: Environ. Res. LNT-Obit.-1.pdf

Clint:

See the article.....please share with your colleagues. It seems appropriate.

Ed

Message

From: Edward Calabrese [edwardc@schoolph.umass.edu]
Sent: 4/30/2018 8:42:49 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]

Clint:

Exactly one year ago I published the paper "Obituary notice: LNT dead at 89 years, a life in the spotlight." in Environmental Research.....I will send you a copy of that paper today.

Ed

Message

From: American Energy Alliance [info=americanenergyalliance.org@mail32.suw91.mcdlv.net]
on behalf of American Energy Alliance [info@americanenergyalliance.org]
Sent: 8/29/2018 2:21:10 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: Now we're getting wonky...

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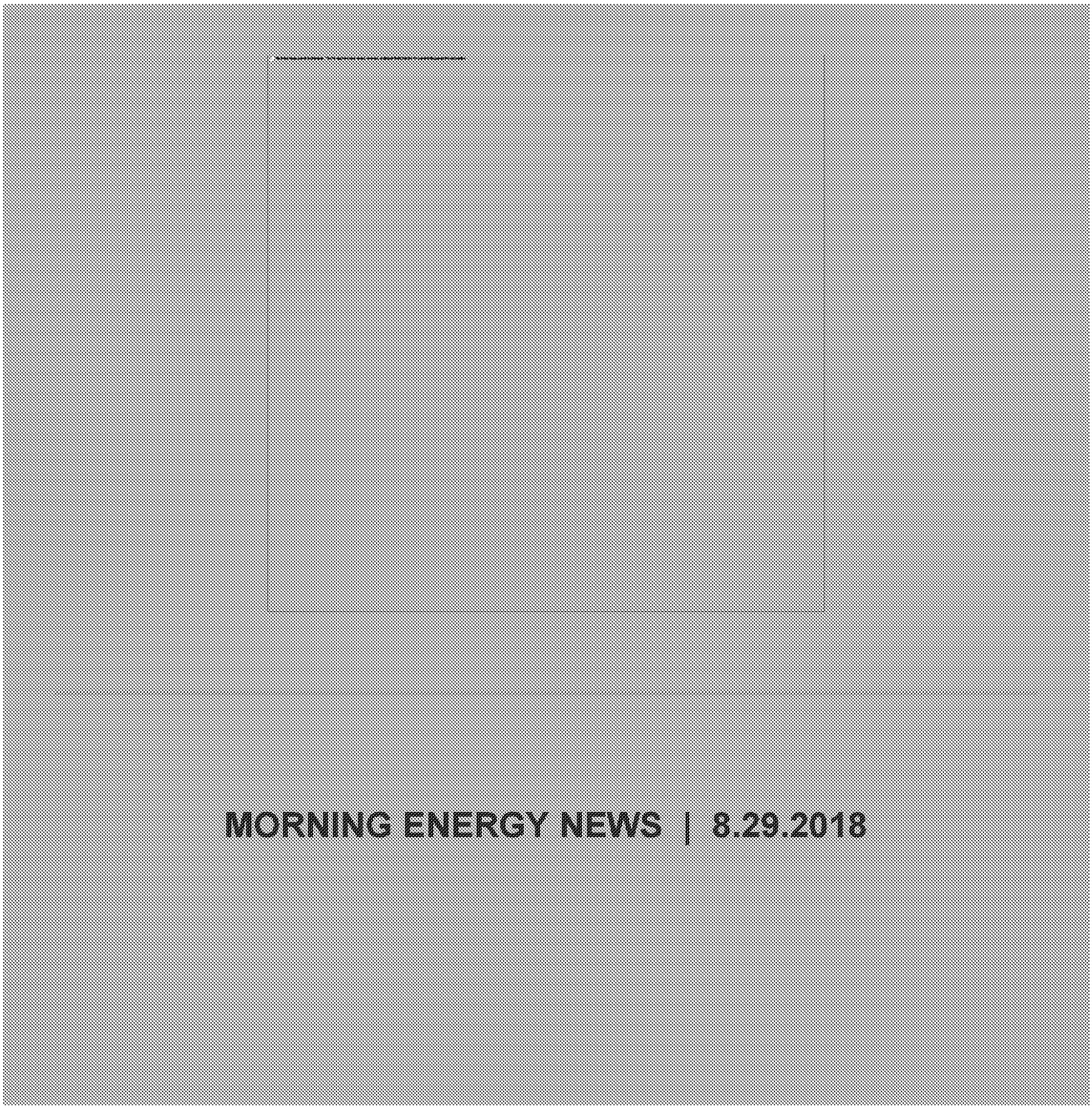
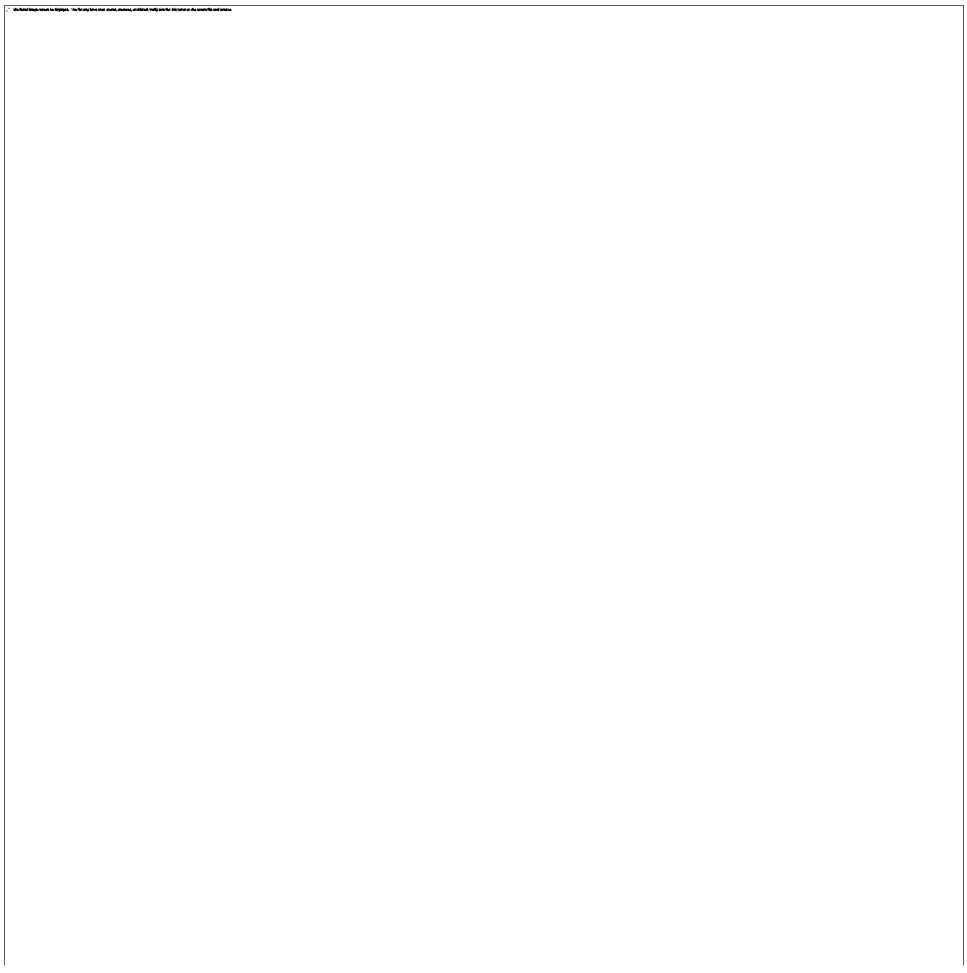
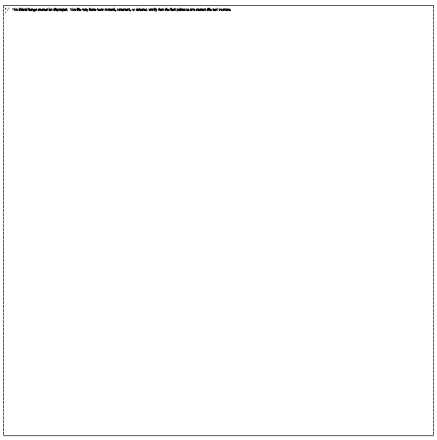


Possibly the single most important change in the regulatory paradigm. Ever.

Cato Institute (8/27/18) blog post: "Since the 1950s, environmental regulations are largely based upon something called the 'linearity-no threshold' (LNT) model, which holds, for example, that the first photon of ionizing radiation has the same probability of causing cancer as the bazillionth one... In fact the LNT model isn't just wrong—nature actually works opposite to it. Small amounts of exposure to things that are toxic in large amounts can actually be beneficial... The alternative model is also largely the handiwork of Dr. Calabrese, which he calls the 'biphasic dose-response,' or 'hermetic' model."





"Capitalism as we know it is over. So suggests a new report commissioned by a group of scientists appointed by the UN Secretary-General. The main reason? We're transitioning rapidly to a radically different global economy, due to our increasingly unsustainable exploitation of the planet's environmental resources."

– Nafeez Ahmed, Vice Motherboard

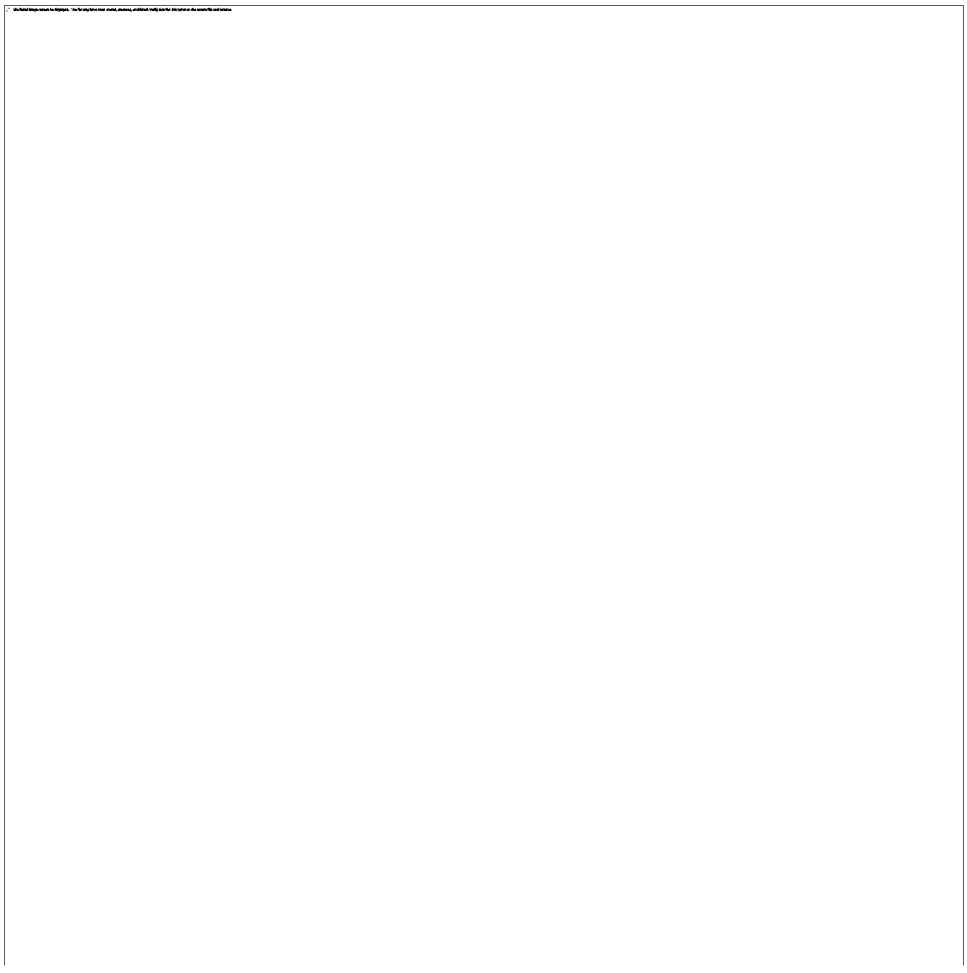
A reminder that politicians are great at destroying economic opportunities for Americans.

The Salt Lake Tribune (8/7/18) reports: "The West's coal country has long

sought to offset declining domestic coal consumption through exports to Pacific Rim countries. But politically liberal West Coast cities and states have gotten in the way, obstructing proposals for new coal-handling terminals. Now, Utah is looking south of the U.S. border to ship its coal and possibly natural gas overseas. On Thursday, the Utah Office of Energy Development (OED) signed a memorandum of understanding with economic development officials for the Mexican state of Baja California to establish 'a close binational collaboration' aimed at connecting Utah energy resources with new markets abroad."

Shocker! The bureaucracy opposes transparency.

The Hill (8/28/18) reports: "The Pentagon is criticizing the Environmental Protection Agency's (EPA) proposal to boost 'transparency' standards for the science it uses in decision making. Patricia Underwood in the Department of Defense's office of energy, installations and environment told the EPA last week that the proposal could unnecessarily exclude sound science from the agency's use."



How the war on climate change hammers the world's poor.

New York Post (8/26/18) op-ed: "Forcing poor countries to reduce emissions does even more harm, because cheap, abundant energy brings prosperity. Example: Activists argue Bangladesh should cut coal expansion. That would deliver global climate benefits worth nearly $100 million. But the forgone boost to the Bangladeshi economy would cost about $50 billion. Aside from the immorality of obliging poor nations to avoid policies that would reduce poverty, the big problem with forcing carbon cuts is that green energy is not yet the savior that it is portrayed as. Even after decades of heavy investment in subsidies to support green-energy production — costing more than $150 billion just this year — the International Energy Agency finds that wind provides just 0.6 percent of energy needs, and solar 0.2 percent."

Energy Markets

WTI Crude Oil: ↑ $69.07
Natural Gas: ↑ $2.86
Gasoline: ↑ $2.84
Diesel: ↑ $3.15
Heating Oil: ↑ $222.55
Brent Crude Oil: ↑ $76.41
US Rig Count: ↑ 1147

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Attachments: mercatus-shamoun-regulation-uncertainty-v1.pdf

https://www.mercatus.org/system/files/mercatus-shamoun-regulation-uncertainty-v1.pdf

Regulation under Uncertainty

Use of the Linear No-Threshold Model in Chemical and Radiation Exposure

Dima Yazji Shamoun, Edward Calabrese,
Richard A. Williams, and James Broughel

September 2016

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Abstract

This paper examines the use of the linear no-threshold (LNT) model in chemical and radiation exposure. The LNT model assumes that exposure to any level of a chemical or radiation is harmful, down to even the last molecule. Used primarily to be "public health protective," the model has been the backbone of chemical and radiation risk regulation for many decades. Given the current state of science and risk management tools, we challenge the notion that using the LNT as the default model is public health protective. First, more and more research has uncovered dose-response relationships that reveal either a threshold or, more importantly, a hormetic response, where exposure to low doses of a hazard actually yields health benefits. Second, given these more realistic alternative dose-response models, risk management tools including risk-risk analysis and health-health analysis show that regulating down to extremely low levels can have negative health consequences when ancillary risks are considered. Risk-risk analysis focuses on how reductions in target risks can lead to increases in risk from substitute chemicals or activities. Health-health analysis explores how costs of compliance are borne in part by consumers who are forced to reduce their own private risk-mitigating activities. Overestimating risk, a common feature of the LNT model, upsets the careful balancing of risks required of risk managers.

JEL codes: D62, D81, I18

Keywords: linear no-threshold, dose-response, health and safety regulations, benefit-cost analysis, risk assessment

Author Affiliation and Contact Information

Dima Yazji Shamoun
Associate Director of Research
Center for Politics and Governance
Lecturer, Economics Department
University of Texas at Austin
dshamoun@utexas.edu

Edward Calabrese
Professor of Toxicology
University of Massachusetts at Amherst

Richard A. Williams
Director, Regulatory Studies Program
Mercatus Center at George Mason University

James Broughel
Research Fellow, State and Local Policy Project
Mercatus Center at George Mason University

Regulation under Uncertainty:

Use of the Linear No-Threshold Model in Chemical and Radiation Exposure

Dima Yazji Shamoun, Edward Calabrese, Richard A. Williams, and James Broughel

1. Introduction

The linear no-threshold (LNT) model has been the standard risk assessment model used for both chemical and radiation exposure for decades, particularly for low-dose exposure. While many assume that using the model provides for a public health–protective risk management decision, this remains to be proven. This paper challenges the notion that the LNT model is protective of the public health under conditions of uncertainty, in particular with modeling low-dose exposure. The meaning of "public health–protective" becomes less clear when there are offsetting increases in risk either to the target population or to an entirely different population.

We argue that there are three related assumptions, which are central to many risk assessments, that may lead to poor public health decisions: the LNT assumption, which might be thought of as a zero threshold assumption; the zero substitution effect assumption; and the zero income effect assumption. The LNT model, a widely applicable dose-response model in risk assessment—especially in cancer risk assessment—hypothesizes that exposure to even a single molecule of a hazard is sufficient to induce harm. By contrast, a threshold model assumes that exposure up to a certain dose is harmless, and a hormetic model hypothesizes that exposure to low doses of stressors is protective (i.e., beneficial) and only becomes harmful at higher doses.

The zero substitution effect assumption is that there are no risk-risk tradeoffs and, thus, a reduction in a target risk yields no unintended increases (or decreases) in other risks. Finally, the zero income effect assumption is that there are no health-health tradeoffs, meaning that

regulatory efforts to mitigate a target risk yield no offsetting increases in personal risks when private income is reduced by regulatory spending on health and safety.

If any one of these assumptions (or a combination of them) is found to be false, then public health may be compromised. The use of the LNT model, especially with its emphasis on conservatism, may lead to choices that increase the expected cost of risk-risk and health-health tradeoffs. Its widespread use could, for example, contribute to a culture among regulators whereby focus is aimed narrowly at target risks, but to the exclusion of countervailing risks, without consideration of diminishing marginal returns to public risk-reduction attempts, and in ignorance of private risk-reduction efforts.

We begin this paper with a background discussion of the history and origin of the LNT model. We then present a brief review of the recent scientific literature on hormesis, DNA repair, preconditioning, and adaptive responses in biology, challenging the foundational validity of linearity. Finally, we conclude with a discussion of tradeoff analysis, namely risk-risk analysis (RRA) and health-health analysis (HHA), which sheds light on the role of unintended consequences and opportunity costs in magnifying the potential health consequences of using the LNT model. Despite its widespread use, the LNT model is due for a reevaluation. In addition, because much of the health effect we are discussing occurs in the very low dose range, dose-response uncertainty, risk-risk tradeoffs, and health-health tradeoffs should be analyzed as part of risk management to improve public policy decisions and outcomes.

2. Background of the LNT Model

When estimating the risk from exposure to chemical hazards, neither epidemiological nor animal studies generally provide dose-response data in the relevant region for the average

human level of exposure, that is, the low-dose region. Due to the limitations of existing study protocols, extrapolations to possible responses in the relevant low-dose region are usually made from the level of response observed in the high-dose region. The LNT model assumption, which roughly connects the lowest dose-response point observed in animal studies to the origin, is the most common model used for extrapolation. For cancer risk assessments, in particular, it is the regulatory default,[1] and, in effect, it implies that there is no safe threshold for exposure to a carcinogen; exposure to even a single molecule of a carcinogen could cause harm proportional to the dose.

The adoption of the LNT model for cancer risk assessment stands at odds with the founding principle of toxicology that "the dose makes the poison." To quote Paracelsus in full: "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy" (Kirsch-Volders, Aardema, and Elhajouji 2000). Yet the LNT model assumption eliminates consideration of a threshold and focuses only on the level of "presumed" poisonous effects. Recent work, however, continues to affirm the presence of repair, as the body has "demonstrated response to mitigate or eliminate [the] damage" from low dose radiation. (Sacks, Meyerson, and Sigel 2016).

Abandonment of the previously held threshold assumption constituted a significant paradigm shift in toxicology. Although "extraordinary claims require extraordinary proof,"[2] the LNT model was accepted as the default model for cancer risk assessment by US regulatory agencies without an extraordinary justification. In the following two subsections we provide a

[1] Some noncancer risk assessments make use of the LNT model as well, though they are more aberrational than customary. For example, the Environmental Protection Agency applies the LNT model to estimate the risk of exposure to low doses of some air pollutants, such as fine particulate matter ($PM_{2.5}$) and more recently to ozone (O_3).

[2] The original quote may have been from Marcello Truzzi (1987): "The more extraordinary a claim, the heavier is the burden of proof demanded."

brief history of the LNT model and its application by regulatory agencies to ionizing radiation and then to chemical carcinogens in general (a historical summary is provided in the table in the appendix).

2.1. Adoption of the LNT model in the Assessment of Risk of Ionizing Radiation

Ever since the publication of Darwin's 1859 work, *On the Origin of Species by Means of Natural Selection*, the question as to the cause of genetic change by which natural selection takes place has occupied the biology community (Calabrese 2013b). Evolution was seen to be driven by random mutations to individual genes, which would then be passed on to future generations (Muller 1922). But what was inducing the mutations?

Geneticists raced to discover this mechanism of evolution. They applied stressors ranging from temperature to ionizing and nonionizing radiation. In 1927, Nobel Prize–winning geneticist Hermann J. Muller initiated a discussion on the possibility that X-rays could lead to heritable mutations. Though the doses he used in his study were extremely high (200,000 times the background dose), he found a significant mutation rate, which led Olson and Lewis (1928) to speculate that naturally occurring ionizing radiation may be the process behind evolution (Calabrese 2013b).

Even given linearity in the low-dose region, however, the inducible mutation theory was ambitious, as it hypothesized that small doses of natural radiation could explain the full extent of evolution driven by genetic mutation. Despite the need for extraordinary proof and the emergence of several studies rejecting the LNT model interpretation (Patterson 1928), genetic mutation in response to ionizing radiation came to be the common assumption, requiring a new framework to accompany it.

This novel framework would emerge from a collaboration of geneticists and physicists. Before Muller's theory of inducible mutation, medical physicists had envisioned that each cell has a sensitive area, or a heart, and that when the heart dies, the cell dies. According to this theory, known as target theory, cells are dosed with radiation that may result in "hits" that can then kill the cell. A cell can potentially survive a number of radiation doses, as not every dose will hit the heart (of a cell); also the heart may withstand several hits before it dies. Thus, target theories are modeled as x-hit target theory, where "x" denotes the number of hits it takes to kill the heart of the cell. For example, a single hit theory implies that the heart will be killed on the first hit (Nomiya 2013)—that is, response occurs in proportion to the dose.

Applying target theory to radiation-induced mutation advanced both the state of target theory and the LNT model for ionizing radiation. The formal justification of the linear dose response within the target theory framework appeared in an influential paper by radiation geneticist Timoféeff-Ressovsky and physicists Delbruck and Zimmer (1935). The paper hypothesized a binary reaction mechanism where an observable response (i.e., mutation) takes place when units of energy are absorbed (or ionized) by the target region (the particularly sensitive region, or the heart) of a gene. Once an X-ray treatment excites an electron in the target region of the gene, a permanent effect takes place in the form of a mutation (Calabrese 2013b). The units of energy are generally referred to as hits and thus the target theory of ionizing radiation is often referred to as the one-hit target theory.

The one-hit target theory of mutation stood at odds with the general physiological understanding of the time that the elimination of one molecule out of a very large number of molecules does not generate an observable effect. Even after the 1953 discovery of the structure of DNA (Watson and Crick 1953) came to replace most of what had been assumed about gene

structure (e.g., its molecular stability), the one-hit target theory continued to be applied. And in 1956 the theory even made its way to the Biological Effects of Ionizing Radiation I (BEIR I) committee formed by the National Academy of Sciences. There the geneticists comprising the BEIR I panel made the seminal recommendation to switch from a threshold model to a linear model to estimate the risk of mutation from ionizing radiation (Calabrese 2013b).

Still, as understanding of low-dose-induced DNA repair and recovery was making its way through the scientific community, some challenged the BEIR I decision. These challenges, however, did not succeed in reversing the BEIR I decision, and regulatory agencies in America and around the world followed BEIR I's lead, adopting linearity in cancer risk assessment (Calabrese 2013b).

2.2. Adoption of the LNT Model in the Assessment of Risk of Other Stressors

In 1961 Nathan Mantel and W. Ray Bryan used a probit model to estimate the risk of developing cancerous tumors when exposed to carcinogens (Calabrese 2013b). They recommended a "safe dose" of 1 in 100 million. The common regulatory "tolerated" level of risk from exposure to carcinogens traces its origin to this publication. This safe-dose recommendation was adopted by the Food and Drug Administration (FDA) in its publication of the 1973 risk guidelines, but it was modified to 1 in 1 million in 1977.[3] In 1979, the FDA revised its cancer risk assessment policy, replacing the probit model used by Mantel and Bryan with the LNT model.[4]

---

[3] The 1 in 1 million level was the threshold below which no regulatory action was necessary.

[4] In fact, there have been many mathematically based models used to extrapolate from high to low dose for carcinogenesis. One significant method used by the EPA early on came from K. S. Crump (1984). There were two-stage models (Armitage and Doll 1957), three-stage models (Neyman and Scott 1967) and the one-hit model from Moolgavkar and Venzon (1979) and Moolgavkar and Knudson (1981). These are discussed in Thorsland, Brown, and Charnley (1987). A more general discussion can be found in Anderson and the Carcinogen Assessment Group of the EPA (1983). For a thorough analysis of the history and evolution of dose-response modeling, see Calabrese (2013b).

The EPA took several measures in the 1970s to limit exposure to carcinogens.[5] In its 1976 proposed guidelines on carcinogenic risk, the EPA recommended the use of quantitative risk assessments to estimate the risk of exposure to carcinogens. Based on limited epidemiological evidence on ionizing radiation and the link between smoking and lung cancer, the EPA also endorsed the use of the one-hit model (and thus a linear dose response) (Calabrese 2013b). According to EPA Administrator Douglas Costle, the one-hit model was chosen due to its conservative nature, that is, its perceived bias toward overestimation of risk in the presence of uncertainty (EPA 1976). Overestimation of risk was (and still is) considered consistent with the agency's mission to protect public health from environmental chemical exposures. A later publication suggested that wide application of the LNT model in regulatory risk assessment was due in part to its attractiveness to regulators, namely, "It is easy to apply and . . . it will generate an upper bound on the unknown, underlying cancer risk in most instances." (Office of Science and Technology Policy 1986). And the timing for the regulation of chemical carcinogens was simply right, following as it did on the heels of ionizing radiation, a mutagen with a readily available and widely used framework of analysis. So while the one-hit model was initially proposed for the mutational effects of ionizing radiation, it eventually became the default model for all chemical carcinogens.

In 1977 the Safe Drinking Water Committee (SDWC) of the National Academy of Sciences (NAS) recommended to the EPA the adoption of the LNT model in cancer risk assessment (Calabrese 2013b). The EPA followed this recommendation in 1979 in its assessment of the risk of chloroform in drinking water (Environmental Protection Agency 1979). The

[5] The EPA's website has a Quantitative Risk Assessment for Exposure to Vinyl Chloride (Kuzmack and McGaughy 1975) and Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens (Train 1976).

SDWC expressed skepticism on the grounds that the LNT model did not incorporate biological characteristics of the animal studies nor did it anticipate "newer developmental methodologies" (Calabrese 2013b). As a result, the SDWC briefly withheld its endorsement of the LNT model only to endorse it again in 1983, since the model was still in use by the EPA. From there, the LNT model became the default methodology for the assessment of risk of chemical carcinogens. These endorsements and the application of the LNT model, first by the FDA (1979) and then by the EPA (1979), were foundational steps in the history of regulatory risk assessments.

3. Recent Developments in Dose Response

Regardless of the reasons why regulatory agencies initially decided to use the LNT model, the debate should now be on whether there is sufficient evidence to justify maintaining its use. As we argue, there is mounting evidence in biology and toxicology (as well as risk management theories) to support reevaluation of the choice of dose-response model to optimize public health. The LNT model is difficult, if not impossible, to validate and, therefore, integrating other default models may allow for conducting validation exercises. Evidence of alternative dose-response models (e.g., hormesis) and biological mechanisms (e.g., DNA repair, preconditioning, and adaptive response) suggest that adherence to the LNT model may be imprudent, as it prevents public policy from achieving its full potential in protecting public health.

In fact, due to these issues of validation and plausibility, the Nuclear Regulatory Commission has recently started examining the validity of the LNT model as compared to the hormetic model for ionizing radiation (Nuclear Regulatory Commission 2016). In the next section we briefly outline three challenges from toxicology and biology to the LNT model,

namely, validation issues, hormesis as an alternative model, and, finally, research on DNA repair, preconditioning, and adaptive responses in biology.

3.1. Validation Issues

As noted above, it is extremely difficult, if not impossible in some instances, to validate the dose-response function at low doses, since thousands of subjects are required to uncover either a small response or a relatively infrequent event. This is particularly true when the adverse effect, such as cancer, occurs in both the test and the control group (Scala 1991). This task is made even harder when one potential response in the test group is a decrease in the incidence of the adverse event, that is, a hormetic response. To uncover such an effect would require a study design that would allow for such a response. Another difficulty for a dose-response researcher, and the more familiar one, is extrapolation. Extrapolation problems exist for both animal and human (epidemiological) studies. Even the most sophisticated epidemiological and animal studies are incapable of detecting low levels of risk, for example, below 1 percent, and so these risks must be imputed based on data at higher doses.

The validation issue is further magnified with the LNT model, as it predicts proportional risk to ever smaller and smaller doses. Much of the current justification for using LNT as the default dose-response model for exposure to ionizing radiation and chemical carcinogens is rooted in epidemiological studies. However, epidemiological studies are difficult to reproduce, hard to map to the general population due to the presence of confounders, and are often focused on cases where the population in question is exposed to high dose levels (Taubes 1995). Examples of such cases are studies of the effect of ionizing radiation that rely on evidence from radiation exposure following Hiroshima, Nagasaki,

Chernobyl, and Fukushima; occupational radiation studies; and medical studies on highly exposed individuals (Calabrese and O'Connor 2014).

Such high-dose exposure events and studies are therefore unsuited for extrapolation to the relevant day-to-day low-dose events like the use of X-rays and CT scans for medical purposes (Berrington de González et al. 2009). Even some of the more recent articles in the medical literature that predict high rates of disease and cancer-related deaths due to medical imaging in the United States rely on extrapolation from high-dose exposure to radiation (Berrington de González et al. 2009; Abbott 2015).

Moreover, there is a sizable stock of scientific research (epidemiological and medical) suggesting the possibility of a threshold model for radiation exposure for doses below 100 mSv (Ropeik 2013), while other studies have detected a beneficial response to low-dose exposure. For example, four epidemiological studies of subjects who are naturally exposed to background radiation did not detect any increase in cancer risk, with one study detecting a positive response to low-dose radiation (Tao et al. 1999).[6] Another study on the effect of radon exposure revealed beneficial effects to low-dose exposure (Cohen 1995). These results were affirmed in another more recent study on radon exposure, which detected the possibility of positive effects from low doses of radiation on lung cancer (Thompson et al. 2008). A multiple-country analysis of occupational exposure to X-rays and gamma-rays in nuclear power plants also did not detect negative health effects from exposure in workers; instead it showed a rate of all cancer mortality lower in the exposed workers relative to the general population (Cardis et al. 2007). A quick search on Google Scholar for hormesis alone generates 23,800 articles.

[6] The lack of statistical significance in these studies is nonetheless important, as it means that the effect of exposure to low-dose radiation on cancer risk is not different from zero. This finding of non-significance may imply a possible threshold and not an LNT model.

Much of the aforementioned research, which was unable to validate a linear response, also relies on epidemiological, occupational, and ecological investigations, which naturally suffer from the same shortcomings as the studies *supporting* linearity. Yet, regulatory risk assessment has lacked a systematic review of the evidence in support of each model. Such a review could shed light on the weight of evidence in support of each model while accounting for study design and quality. For example, lack of a systematic review is illustrated by the seventh committee on the Biologic Effect of Ionizing Radiation (BEIR VII) that attributed the beneficial response in the multiple-country study of occupational exposure to X-rays and gamma-rays to a "healthy worker effect and unknown differences between nuclear industry workers and the general public" (Calabrese and O'Connor 2014). These kinds of assertions are not helpful when equally plausible alternative explanations exist, but are ruled out without any review of the existing evidence.

The difficulty of validating models at very low doses drove the Health Physics Society and the American Association of Physicists in Medicine (AAPM) to conclude in December 2011 that the effects of radiation at very low doses (50–100 mSv) are either too minuscule to detect or virtually nonexistent. As a result, the two organizations issued statements recommending against quantitative estimation of health risks for doses of radiation below 50 mSv annually or below 100 mSv above that of background radiation in a lifetime. In the words of the AAPM (2011),

> Risks of medical imaging at patient doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predications of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged. These predictions are harmful because they lead to sensationalistic articles in the public media that cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures.

As outlined, the low-dose region is one saturated with uncertainties and the choice of one model to estimate health risks gives "a false sense of precision" (Office of Management and Budget 2007) where none currently exist. Given that the use of the LNT model may lead to poor public health decisions, then integrating it with other plausible dose-response models moves us closer to optimizing public health protection (Calabrese et al. 2015).

The issue of model uncertainty and model validation in the low-dose region has been a challenge for decades. Ever since the publication of *Risk Assessment in the Federal Government: Managing the Process* in 1983 by the National Research Council (NRC), the choice of the low-dose model must be given to the one with the most biological plausibility (National Research Council 1983).

In the next subsection, we present recent developments in biology that support another low-dose model, namely, hormesis, or the biphasic dose-response model. In addition to having more biological support than the LNT model, hormesis, if correct, casts doubt on the supposed conservative nature of LNT.

3.2. Hormesis

In contrast with the LNT model, the hormetic dose-response model is a biphasic model where direction of response is not constant across doses. While response to exposure to a high dose of some substance may indeed be proportional to dose (i.e., harmful), response to exposure to a low dose of the same substance may be *inversely* related to dose (i.e., protective). In other words, exposure to a low dose of a carcinogen may—up to a certain threshold—*lower* the risk of developing a particular cancer. These characteristics are sometimes described as low-dose stimulation and high-dose inhibition.

As previously mentioned, all dose-response models encounter validation problems in the low-dose region; hormesis faces this issue as well. In hormesis, the hormetic effect is generally modest, that is, 30–60 percent greater than control values (Calabrese and Baldwin 2003). Given the small ratio of signal to noise and the modest effect, it is difficult to replicate hormesis and to distinguish between a threshold and a hormetic model in the low-dose region respectively (Calabrese and Mattson 2011). Considering, however, the significance of health implications of correctly identifying the type of dose-response model, efforts to design better studies have continued. As described in one paper, "The use of different default models has important implications in many areas, including the establishment of limits for chemical exposures" (Calabrese 2008).

Recent advances in clinical studies have begun to allow researchers to overcome some of the aforementioned obstacles. For example, shifting focus from whole-animal to cell-level investigation has allowed for more doses to be tested and results to be replicated, in addition to both allowing results more relevant to humans and to relying less on extrapolation (FDA 1993). These and other recent advances suggest that the dynamics of the low-dose region may be more nuanced than is predicted by the default LNT model.

Hormesis has been found to make more accurate predictions than both the LNT and threshold models using large independent data sets (Calabrese and Baldwin 2003). Some research has provided an explanation for the mechanism of action of hundreds of hormetic dose responses, suggesting that hormesis may be more of a rule than an exception. This claim was extended to both cancer and noncancer end points and is said to be independent of the biological model and the stressors tested (Calabrese and O'Connor 2014).

Studies in toxicology have revealed hormetic dose responses for both ionizing radiation and chemical carcinogens. One estimate for chemicals found a hormetic response in 37–50 percent of chemicals tested and also found that the hormetic responses exceeded those of the threshold by 2.5 to 1 (Calabrese and Baldwin 2003). In fact, a hormetic response is detected in nearly 2,000 chemical agents from a broad range of chemical classes (Calabrese et al. 2008, Calabrese 2013a). Some of the studies showing a beneficial health effect of ionizing radiation at low levels of exposure (discussed in the previous subsection) may also be an example of a hormetic dose response.

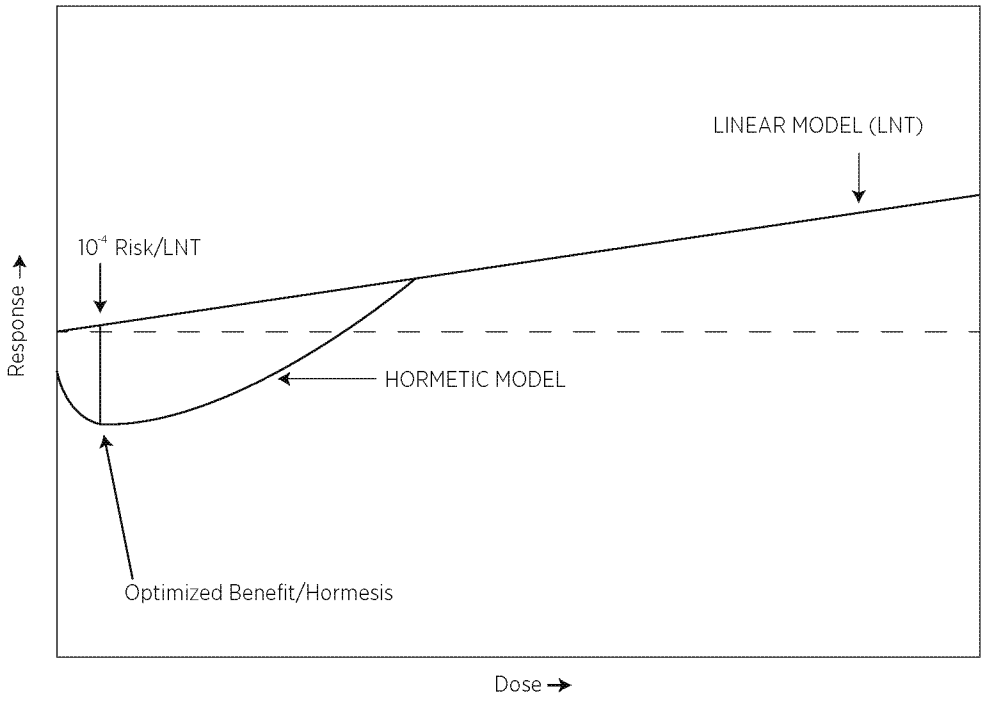
A major FDA-funded study (the mega-mouse ED01 study), which included 24,000 animals exposed to a known carcinogen (2-acetylaminofluorene, a derivative of fluorene), found evidence supporting a hormetic, or biphasic, dose response (Bruce et al. 1981). Additionally, a reassessment of the effect of DDT in an animal study—on which regulatory agencies had based their risk assessment—revealed a hormetic dose response (Sukata et al. 2002). Hormesis has also been detected in exposure to low doses of air pollutants, namely particulate matter (Cox 2012).

The LNT model is often argued for and justified on the basis that it is a conservative approach (EPA 2005).[7] However, hormesis alone casts doubt that adherence to linearity is necessarily conservative as we intervene to maintain lower doses. As recent research on model

[7] Some claim that the LNT model is not conservative. For example, Bailar et al. (1988) argue that a supralinear dose-response relationship is possible for some chemicals. Others have argued that the human population is heterogeneous in its susceptibility to cancer risks (Finkel 2014), such that some individuals will experience higher than average cancer responses. Bailar et al. (1988), however, did not consider the possibility of a J-shaped dose response in his study due to its lack of support at the time. Now, however, ample support for a J-shaped dose response is available, as mentioned above. Regarding variation in human susceptibility, at least for the purposes of calculating benefits in a benefit-cost analysis, it is the mean response in the population that should be considered. Some individuals will no doubt experience higher than average cancer responses, just as others will be lower than average. As will be discussed in more detail below, taking an upper bound of risk that accounts for humans having higher than average susceptibility or having a higher exposure is not conservative because there is a balance to be struck between target risks and the risks associated with risk-risk tradeoffs and health-health tradeoffs. Such balancing is impossible when upper bounds are used in place of mean population responses. Further, research on the integration of hormesis and the LNT model shows that setting a protection standard based on the response of the most sensitive populations can lead to a net negative health outcome (see Calabrese et al. 2016).

uncertainty suggests (Calabrese et al. 2015), the optimal hormetic response occurs at the nadir of the hormetic curve, which is illustrated in figure 1. As argued, the dose corresponding to a 10^{-4} response according to the LNT model is roughly aligned with the dose yielding the optimal hormetic response. Therefore, seen in light of model uncertainty and if the hormetic model is correct, then pushing exposure to a dose smaller than the dose corresponding to a 10^{-4} response as predicted by the LNT model will yield net health harm. Taking bladder cancer as an example, the health gains achieved by pushing exposure to a dose corresponding to a 10^{-6} LNT response (i.e., 100 bladder cancers less than a dose corresponding to a 10^{-4} LNT response), will be dwarfed by the health harm induced by eliminating the potential for protective hormetic effects (i.e., 3,150 more incidences of bladder cancer) (Calabrese et al. 2015).

Figure 1. Model Uncertainty and Health Protection when Accounting for Hormesis



Source: Edward J. Calabrese, Dima Y. Shamoun, and Jaap C. Hanekamp. 2015. "Cancer Risk Assessment: Optimizing Human Health through Linear Dose-Response Models." *Food and Chemical Toxicology* 81: 137–40.

3.3. DNA Repair, Preconditioning, and Adaptive Responses in Biology

When the LNT one-hit model was first proposed, it was assumed that a single change of DNA could initiate the carcinogenesis process and damage could not be reversed. In other words, DNA repair was ruled out. Scientific understanding has come a long way since then. In addition to recent developments indicating that displacing a large number of molecules is required to affect a mutational event (Weiss 1944), several types of cells are now found to successfully repair mutated DNA (Hanawalt 1994). And even if a carcinogen can initiate a carcinogenesis process in a linear fashion, the development of tumors may not necessarily follow. For instance, in one study Driver, White, and Butler (1987) demonstrated that a single administration of the mutagen/carcinogen dimethylnitrosamine (DMN) induced a linear dose response for renal mesenchymal DNA adducts (early cancer process stage), as well as for mesenchymal foci (later cancer process stage), observations consistent with the LNT model. However, the linear transition to the occurrence of tumor formation was not observed, as the foci at the lower doses failed to proceed to the tumor stage, yielding a threshold, rather than a linear dose-response relationship.

A similar point was made in a 1990 paper by Ames and Gold. The authors argued that cell division plays an important role in the carcinogenesis process, as cell division increases the vulnerability of DNA to mutation. Since animal testing is very expensive, rodents are generally subjected to chronic doses of hazards in order to better detect a carcinogenic effect. However, when high doses of a carcinogen are being administered in an acute manner—causing the destruction of some cells—then cell division is the natural bodily reaction to replace these dead cells, making DNA mutation more likely. As Ames and Gold have observed,

> By causing chronic cell division, a high percentage of all chemicals might be expected to be carcinogenic at chronic, near-toxic doses. . . . About half of all chemicals tested

> chronically at the MTD [maximum tolerated dose] are carcinogens. The fact that about 40% of rodent carcinogens are not mutagens is consistent with our understanding of the important role of cell division in carcinogenesis. Although toxicity at or near the MTD often induces cell division, below a certain dose no such effect is observed. (Ames and Gold 1990)

Research on DNA repair offers a significant challenge to the LNT paradigm: The notion of self-repair is inherently inimical to a linear theory. But while it could be argued that DNA repair does not on its own resolve the debate over the dose-response model, recent biological research on preconditioning and adaptive response seems to make a convincing case for hormesis.

Preconditioning and adaptive response research explores whether a low dose of a stressor induces a protective reaction in the body against higher doses of the same stressor and, in some cases, higher doses of other stressors. In other words, low doses of a stressor can increase resilience and promote survivability in the environment. Stressors can vary from environmental pollutants to chemical carcinogens to exercise to intermittent fasting. The ability of organisms to react adaptively to low doses of stressors has recently been argued to play a fundamental role in evolution (Mattson and Calabrese 2010). In fact, preconditioning and adaptive response is challenging two fundamental implications of the LNT model, namely that dose is cumulative and damage is irreversible (Calabrese 2015, Calabrese 2016).

Research on preconditioning and adaptive response is now proposing less invasive methods, both to treat present diseases and to prevent susceptibility to future ones. Recent studies argue that low doses of X-rays can induce a protective effect to treat pneumonia by promoting an anti-inflammatory response (Calabrese, Dhawan, and Kapoor 2014). Moreover, low-dose radiotherapy is argued to be highly effective on patients with shoulder tendonitis or bursitis (Calabrese, Dhawan, and Kapoor 2014). Low-dose X-rays have also been asserted not only to initiate an adaptive response to higher doses of radiation but also to nonradiation stress, such as oxidative damage,

which constitutes a major cause of diabetic complications. Low-dose radiation has been found to induce a maximal protective effect against kidney damage in diabetic patients (Shao et al. 2014).

Other research examines low-dose light therapy administered to the front lobe of the brain to stimulate brain and muscle activity and to sharpen memory (Hayworth et al. 2010). Additionally, low-level light therapy (LLLT) has been shown to be an effective treatment against subsequent heart attacks, and when administered to patients before surgery, it can promote healing of surgical wounds. In addition, LLLT administered on normal muscles may increase the amount of physical work that can be performed by extending the time that the muscle can function comfortably before fatigue starts (Agrawal 2014).

A comprehensive review of all the recent research on preconditioning and adaptive response and the biological basis of hormesis is beyond the scope of this paper, but one such study is Calabrese (2008). It is clear, however, that hormesis and preconditioning play substantial roles in public health. While massive uncertainties may fog up the low-dose region and make model selection a challenging endeavor, biological plausibility—as advocated by regulatory agencies and the NRC for many decades—must be the tiebreaker.

4. A Methodology to Alleviate the Uncertainty of Regulation in the Low Dose

Guidelines from the National Academy of Sciences can assist when reevaluating critical assumptions such as the LNT model. In addition, the NRC has dedicated numerous publications to risk assessment over the past three decades. For example, in 2009 the Council released *Science and Decisions: Advancing Risk Assessment* in which an entire chapter was dedicated to the "Selection and Use of Defaults." Choosing scientific defaults has been defined as "trans science," that is, "questions which can be asked of science and yet which cannot be answered by science" (Wagner

1995). By their nature, then, many of the default assumptions on which regulatory agencies generally rely in their risk assessments have been subject to controversy over the years (National Research Council 2009). This problem has been recognized in NRC publications dating back to the 1983 *Risk Assessment in the Federal Government: Managing the Process*—the famous Red Book—and the 1994 *Science and Judgment in Risk Assessment.* In the chapter on defaults in the 2009 publication, the NRC makes the case for selecting sound default assumptions as summarized in the following four recommendations (National Resource Council 2009):

1. Have a clear choice of defaults to prevent inconsistency resulting from an ad hoc interpretation of the data across the agency's analysis. Further, a default assumption may be well chosen in general, but it is necessary to maintain flexibility in the application of defaults, as substance-specific data may justify a departure from defaults.
2. Invoke defaults for the steps of the risk assessment where it is necessary to make "inferences beyond those that can be clearly drawn from the available data or to otherwise fill common data gaps." "Inferences are needed when underlying biologic knowledge is uncertain or absent."
3. Maintain criteria "available for judging whether, in specific cases, data are adequate for direct use or to support an inference in place of a default."
4. Report and compare alternative risk estimates in the presence of a "comparably plausible" alternative assumption; abandon a default assumption in favor of an alternative assumption when the latter is determined to be "clearly superior" to the former, that is, "its plausibility clearly exceeds the plausibility of the default."

The NRC makes the analogy between the "clearly superior" standard for alternatives to the legal concept of "evidence beyond reasonable doubt." A similar analogy can be drawn for

this point where "comparably plausible" can be interpreted as the legal parlance "preponderance of evidence," or the 50 percent range of plausibility. The two points can be reasonably summarized as follows: when an alternative is comparatively plausible, quantitative model uncertainty should be characterized and presented in the risk assessment; on the other hand, when an alternative is clearly superior, it should, then, replace the default. The NRC further clarifies the *clearly superior* standard by saying, "The term *clearly superior* should not be interpreted quantitatively, but the committee notes that statistical P values can also be used as an analogy. For example, rejecting the null in favor of the alternative only when $P < 0.05$ could be viewed as insisting that the alternative hypothesis is 'clearly superior' to the 'default null.'"

In a manner consistent with the recommendations from the NRC outlined above, regulatory agencies can make a well-justified fresh assessment of their LNT default assumption. Though choosing a default may be necessary in cases where data is lacking, the NRC encourages abandoning a default for an alternative when evidence accumulates and identifies the alternative as a more appropriate assumption. To follow an objective process for determining the appropriate default, regulatory agencies should consider both bodies of evidence validating the LNT, threshold, and hormetic models. Specifically, regulatory bodies can base their decision on a systematic review of evidence methodology[8] to determine whether hormesis is a "comparatively plausible" or "clearly superior" alternative model to LNT.

If neither the LNT nor the hormetic model are deemed "clearly superior," and the systematic review instead reveals them to be "comparatively plausible," then regulatory agencies

[8] Systematic review of evidence, instead of weight of evidence, is the latest recommendation from the NRC (National Research Council 2011).

can develop a quantitative model uncertainty analysis in their risk assessment and update their protection standards accordingly.[9]

The LNT model has long been the model of choice for cancer (and since 2009, for $PM_{2.5}$) risk assessment. Choosing and adhering to a particular dose-response model may have been necessary for many reasons: to ensure consistency in analysis and avoid ad hoc interpretation of the data; to prevent halting valuable scientific inquiry in the face of scientific uncertainty or lack of technical ability; or to ensure protection of public health and safety when knowledge and consensus are lacking. As argued in this paper, however, since certain assumptions may drive much of the results of a risk assessment, periodic reflection on the choice of assumptions is necessary to ensure that the resulting risk management decision is optimal, given the existing information.

5. Implications of Tradeoff Analysis

The analysis of tradeoffs is foundational to economics and sound decision-making. Tradeoff analysis looks at the consequences of making a choice or taking an action. Every choice taken eliminates another choice that could have been taken instead, and every choice taken has both intended and unintended consequences. Tradeoff analysis, therefore, attempts to calculate how the weight of the intended consequences of an action taken compares to the weight of the unintended consequences of that action as well as the weight of consequences of forgone alternative actions.

Below we will discuss two types of tradeoffs, namely, risk-risk and health-health tradeoffs, which are essential for consideration in any risk analysis based on an LNT hypothesis.

[9] One proposal on how LNT and hormetic models can be harmonized to maximize public health protection is suggested in Calabrese, Shamoun, and Hanekamp (2015).

5.1. Risk-Risk Tradeoffs

The doctrine of better safe than sorry is commonly invoked to justify the use of the LNT model because the "conservative" LNT is more likely to overestimate average risk than a threshold or a hormetic model, but it isn't so simple. Any regulation of risky behavior can push consumers into other, sometimes riskier, behavior. Thus, it is important not to develop tunnel vision, focusing only on the risk at hand. Risk policies must always take risk tradeoffs into account and, at a minimum, ensure that there are no negative public health consequences.[10]

A risk-risk tradeoff happens when risk-reducing actions increase (or decrease) a non–target risk at the same time that a target risk is decreased. These changes in non–target risks—so-called countervailing and coincident risks—are usually unintended but are also often discoverable. Any risk management action will cause people to make different choices, whether because of a change in relative prices or because of a need to employ a different technology (Williams and Thompson 2004).

Risk-risk analysis (RRA) is a formal analytical framework that compares reductions in target risks with unintended increases or decreases in other risks resulting from the mitigation efforts. Countervailing risks are the negative side effects of risk mitigation efforts, while coincident risks are those risks that are likely to fall in tandem with the target risk. A popular example of a risk-risk tradeoff is the increase in the risk of a stomachache as a consequence of taking aspirin to reduce the risk of a headache continuing (Graham and Wiener 1995).

RRA frequently involves both risk assessment and economic analysis, so it must involve a combined effort of risk assessors and economists (Williams and Thompson 2004). Risk-risk

[10] There may be an overall positive public health change resulting from a risk decision that may still fail a benefit-cost test because of non–health-related costs.

tradeoffs add to the uncertainty surrounding the choice of a dose-response model because they complicate the effort to identify a public health-protective policy. Just as there are many low-dose response functions that could be derived from high-dose animal studies, so too there could be many behavioral responses induced by a new regulation. Exposure to new risks as one takes actions to avoid proscribed risks can turn a regulatory action into a public health hazard.[11]

Thus, the issue of whether changes in exposure to risks are producing public health negative or positive outcomes is complicated. As we move to reduce exposure to one hazard, other risks will increase; the crucial risk management question is whether countervailing risks will increase by more than the targeted and coincident risk reductions. We suspect, as do Graham and Wiener, "that risk tradeoffs are quietly hindering the effectiveness of the national campaign to reduce risk" (Graham and Wiener 1995). If we ignore these countervailing risks, we increase the chances of moving in the wrong public health direction. The uncertainty with LNT models acknowledged by considering risk-risk tradeoffs is illustrated in figure 2.

Often, a countervailing risk will result from people using a substitute compound for the one being regulated. Looking at figure 2, if we presume that the target and the substitute both have LNT dose-response curves, then our concern is how the reduction in exposure to the target hazard (from A to B)—which results in a change in risk (here a decrease in response from 1 to 2)—compares to the risk posed by the use of the substitute compound (here an increase in dose from C to D with an increase in response from 3 to 4). The issue becomes even more complicated when there is the possibility that the target or the substitute compound or both might possibly have a hormetic dose-response function. This possibility is illustrated in figure 3.

[11] For example, an FDA warning label requirement for raw unpasteurized juice resulted in juice being pasteurized or ceasing to be produced rather than in the addition of the warning labels (Food and Drug Administration 1998).

Figure 2. Uncertainty Created by Risk-Risk Tradeoffs, Assuming an LNT Model

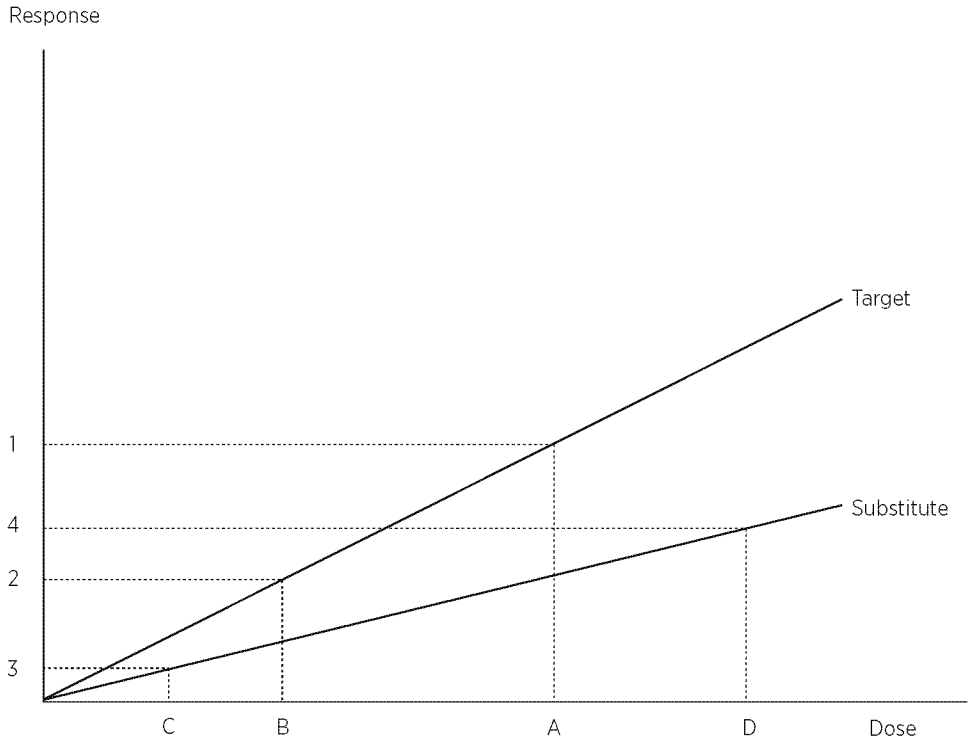
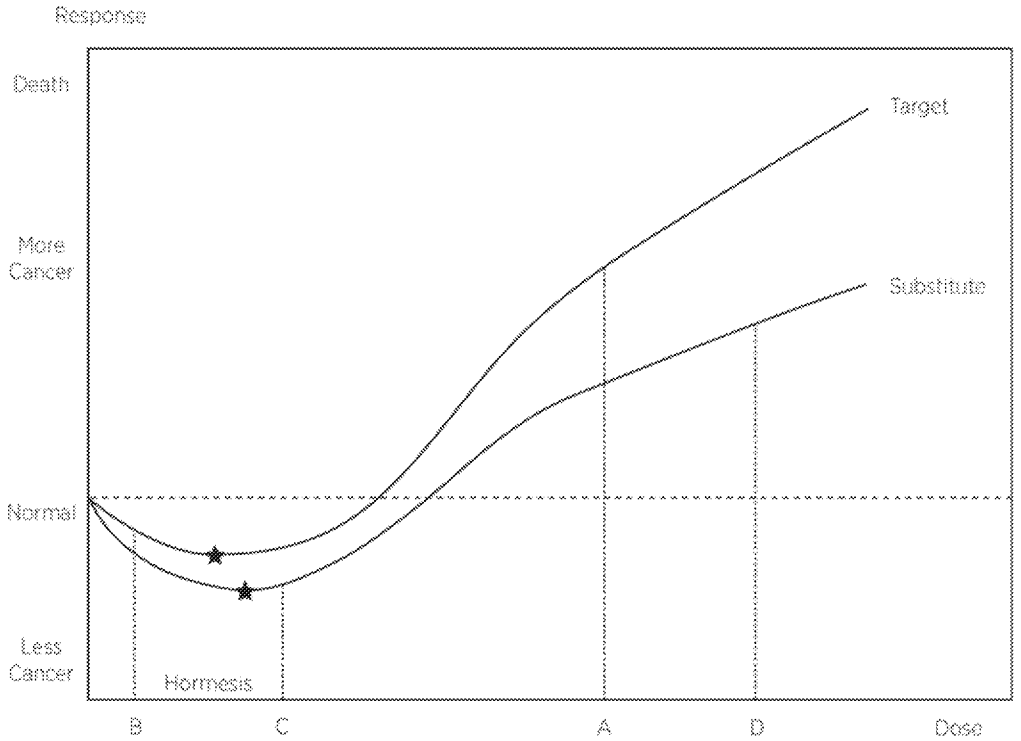


Figure 3. Uncertainty Created by Risk-Risk Tradeoffs, Assuming Hormesis



The stars at the bottom of the two curves represent the apex of the hormetic effect—that is, the optimal health response point. In this example, a decrease in exposure to the target compound from A to B not only decreases risk, it also increases the likelihood of a positive hormetic response, although past the optimal level. For the substitute compound, moving from C to D loses both the protective hormetic response *and* increases risk. Predicting the net effect on risk requires a great deal of information. Without such information, uncertainty may be so great as to make it unclear whether reductions in exposure to the target risk are producing public health positive or negative outcomes. Furthermore, the uncertainty involved in the shape and position of these functions on the two-dimensional dose-response plane makes decisions to improve public health considerably more uncertain.[12]

5.2. Health-Health Tradeoffs

As a general rule, the lower the level at which the mandated exposure to a risk is set, the higher the marginal cost of that mandate is likely to be, due to the economic phenomenon known as diminishing marginal returns. Since a large percentage of regulatory costs are translated into higher prices for goods and services, consumers will have lower real incomes and thus be less able to afford reducing the risks most relevant to them. The lower the levels of exposures chosen, the more it costs to comply (per unit of risk reduced) and the resulting higher prices reduce expenditures on private risk mitigation.

A subset of risk-risk analysis, known as health-health analysis (HHA), focuses on those countervailing risks that occur when regulatory costs reduce private expenditures that address

[12] Of course, consideration of the combined effects of multiple stressors, i.e., additive, antagonistic, and synergistic effects on either risk or hormetic effects, only further complicates the uncertainty.

personal health risks (Lutter and Morrall 1994). This effect alone can render a policy harmful to public health and, as discussed below, can also be regressive.

Vanderbilt Professor Kip Viscusi estimates that for each additional dollar of income earned (or lost), people tend to increase (or reduce) health-related expenditures by 10 cents; that is to say, an individual's marginal propensity to spend on health is roughly equal to 10 percent (Viscusi 1994). As people are obligated to incrementally spend more and more resources complying with regulations addressing public risks, they will respond by reducing expenditures on mitigating risks that they face in their private lives. At some point, if one takes enough income away from people and these losses are spread out across a large enough group, countervailing risks will increase by an amount sufficient to result in expected fatalities. One estimate of the magnitude of burden sufficient to induce one expected fatality is $92 million in 2016 dollars (Viscusi 1994).[13]

Such fatalities are not likely to be distributed evenly across society. Ralph Keeney has shown that such cost-induced fatalities fall disproportionately on those with lower incomes, including some minority groups (Keeney 1994). Conversely, if health and safety goods have diminishing marginal effectiveness, then spending the first dollars yields the largest return (e.g., spending on doctor's visits before spending on a car with a rear-view camera), which, in turn, means that the dollars spent by the lower-income population are the most effective at reducing health and mortality risks. As such, it is important to consider distributional effects in terms of who is bearing the costs and who is enjoying the benefits of risk mitigation. This is a more compelling

[13] This is known as a "statistical fatality" and refers to the adding up of small probabilities of death to one. That is, if 1,000 people stop making expenditures that will prevent a 1 in 1,000 risk of death, then there is the expectation that one "statistical death" will occur, although the identity of the deceased is unknown. The $92 million estimate is adjusted for inflation from $50 million in 1990 dollars, using the Consumer Price Index.

reason why inter-individual variability may be important. Indeed, presidential executive orders currently in effect also require agencies to consider such distributional impacts of regulations.[14] Since many of the benefits of reducing target risks will accrue to concentrated groups of the exposed population, while dispersed populations will realize increases in countervailing risks in addition to the costs of regulatory action,[15] policies with these kinds of differential impacts may be more likely to yield negative public health outcomes in the aggregate.

5.3. Risk and Health Tradeoffs in Practice

An example of how risk-risk and health-health tradeoffs can inform a decision to manage pathogenic risks comes from the consumption of raw oysters. Raw oyster consumption, especially from the warm waters of the Gulf of Mexico, results in approximately 30 deaths each year and more than twice that number of illnesses (Kuchler et al. 1999). One option to reduce this risk would be to restrict consumption of raw oysters during certain months of the year (e.g. March through November) when the pathogen is present at high doses. With perfect enforcement, this would essentially eliminate the target risk of vibrio Vulnificus, the pathogen in question. But two tradeoffs arise.

The first is a risk-risk tradeoff from switching to substitutes, that is, what people eat instead of raw oysters. All foods contain some risk from exposure to microbial, chemical, nutritional, and physical hazards, and there may be other kinds of raw seafood, such as sushi, with which people would replace oysters. One must account for the risks posed by these substitutes.

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[14] See, for example, President Clinton's Exec. Order No. 12866, 3 C.F.R. 76 (1993); President Obama's Exec. Order No. 13563, 3 C.F.R. 58 (2011).

[15] For example, US ethanol rules increased corn prices, which reduced purchasing power for lower-income households around the world (Abdukadirov 2015). The general phenomenon of concentrated benefits and dispersed costs is discussed in Olson (1965).

The second is a health-health tradeoff from reduction in income. Because the typical oyster harvester's job skills are not readily transferable, these individuals would suffer an income loss—perhaps for prolonged periods—if oyster consumption were restricted (Kuchler et al. 1999). Research by Ralph Keeney and others has shown how income loss can cause health problems due to increased alcoholism, depression, and even suicide. Such income effects can lead to a reduction in expenditures meant to reduce personal risks, such as buying safer cars, living in safer neighborhoods, purchasing smoke detectors and baby gates, paying for preventive medical visits, and other risk-reducing products (Keeney 1994).

Pesticide standards are another nuanced example. If banning certain pesticides forces a switch to more expensive pesticides, the price of fruits and vegetables will increase (Gray and Graham 1997). Higher-priced fruits and vegetables may induce marginal consumers to switch to a cheaper but less healthful substitute. The inframarginal consumers, on the other hand—those who elect to keep eating fruits and vegetables despite the higher price—are now made poorer and less able to address their personal risks. Farmers' incomes may suffer as well, due to the higher production costs or a net decrease in demand.

6. Conclusion

Risk assessments were originally meant to give risk managers information that would allow them to choose policies that would unambiguously reduce risks and thereby protect public health. Risk assessments for both radiation and chemical exposure that employ conservative defaults, most particularly the LNT model, seemed to provide a ready-made safe level of exposure to a target risk to achieve this goal. The so-called "safety factors" were also meant to be conservative divisors to accomplish the same effect.

But as regulation has expanded and regulatory exposure limits have reached lower and lower levels, it is no longer possible to ignore the evidence of the biological implausibility of the one-hit model as well as the increasing evidence in favor of hormesis. A default model that inaccurately characterizes risk is a problem not just because the model could be wrong, but also because it could lead to adverse consequences to public health. This follows from the fact that risk management choices must take into account the health consequences of countervailing risks and health-health tradeoffs. These tradeoffs, in some cases, can be sufficient to offset the positive effects of target risk reductions, a consequence that becomes more likely when already-low target risks are overestimated.

Appendix: Major Historical Points Leading to the Adoption of the LNT Model

Year	Author/institution	Event
1859	Charles Darwin	• Publishes *On the Origin of Species*. • Initiates interest in the biological community to determine the cause of genetic change that drives natural selection.
1927	Hermann J. Muller	• X-rays induce mutation in fruit flies.
1928	Olson and Lewis	• LNT model proposed to account for evolutionary changes. • Follows Muller's discovery that X-rays can induce mutations in fruit fly germ cells.
1930	Hermann J. Muller	• Develops proportionality rule (i.e., linear dose response) for ionizing radiation-induced mutagenicity.
1935	Timoféeff-Ressovsky et al.	• Application of radiation target theory for mutagens. • Use target theory to propose a one-hit theory for ionizing radiation-induced mutation. The hit mechanism is used to explain the LNT dose response.
1956	Biological Effects of Ionizing Radiation Committee (BEIR I), Genetics Panel	• Proposes the use of the linear dose-response model for germ cell mutation, using the "doubling rule."
1961	Mantel and Bryan	• Develop carcinogen risk assessment model based on the probit model. • This is undertaken to advise US government agencies on chemical risk assessment.
1973	FDA	• Proposes a probit-based quantitative risk assessment method for cancer risk based on the 1961 Mantel and Bryan paper.
1976	EPA	• Proposes guidelines for cancer risk assessment based on quantitative risk assessment. • Recommends a linear dose-response model.
1977	FDA	• Retains the Mantel-Bryan model with some modifications. • Acceptable risk value is changed to 10^{-6}.
1977	US National Academy of Science's NAS) Safe Drinking Water Committee	• Recommends that EPA adopt LNT model for carcinogen risk assessment. • This recommendation is significant, given the widespread multimedia regulatory functions of EPA. Within two years of the recommendation, EPA applies LNT model to the regulations of trihalomethanes (e.g., chloroform) in drinking water.

continued on next page

Year	Author/institution	Event
1979	FDA	• Replaced the modified Mantel-Bryan model with the LNT model for carcinogen risk assessment, based on the following reasons: ○ Linear procedure is least likely to underestimate risk. ○ Linear extrapolation does not require complicated mathematical procedures. ○ No arbitrary slope is needed to carry out linear extrapolation. ○ Several significant limitations had been found with the application of the Mantel-Bryan model.
1979	EPA	• Establishes a national drinking water standard for trihalomethanes (including chloroform). • This is based on an LNT methodology as recommended by the US NAS Safe Drinking Water Committee (1977).

Note: Table is constructed from discussion in Edward J. Calabrese, 2013. "Origin of the Linearity No Threshold (LNT) Dose-Response Concept." *Archives of Toxicology* 87 (9): 1621–33.

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Message

From: Clint Woods Personal Email / Ex. 6
Sent: 3/28/2018 10:56:35 AM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: Hormesis for Fine Particulate Matter (PM 2.5)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3375488/

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 4/21/2018 7:58:03 PM
To: Edward Calabrese [edwardc@schoolph.umass.edu]
Subject: Re: follow up

Dr. Calabrese,

Absolutely- Hope to have something to you Tuesday afternoon. Thanks so much!

On Apr 21, 2018, at 11:45 AM, Edward Calabrese <edwardc@schoolph.umass.edu> wrote:

> Clint:
>
> If and when the EPA notice is published could you please send me an electronic copy since I might miss it otherwise. Thanks.
>
> Sincerely,
>
> Ed

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 9/14/2018 12:21:50 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Subject: Fwd: Another OAR draft response

Deliberative Process / Ex. 5

Begin forwarded message:

From: "Konkus, John" <konkus.john@epa.gov>
Date: September 13, 2018 at 4:58:28 PM EDT
To: "Woods, Clint" <woods.clint@epa.gov>, "Gunasekara, Mandy" <Gunasekara.Mandy@epa.gov>
Cc: "Yamada, Richard (Yujiro)" <yamada.richard@epa.gov>
Subject: RE: Another OAR draft response

Deliberative Process / Ex. 5

Find more information here: https://www.epa.gov/radiation/radiation-health-effects

---

From: Woods, Clint
Sent: Thursday, September 13, 2018 4:55 PM
To: Konkus, John <konkus.john@epa.gov>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>

Cc: Yamada, Richard (Yujiro) <yamada.richard@epa.gov>
Subject: RE: Another OAR draft response

+ Yamada

Deliberative Process / Ex. 5

From: Konkus, John
Sent: Thursday, September 13, 2018 4:27 PM
To: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>; Woods, Clint <woods.clint@epa.gov>
Subject: Another OAR draft response

Deliberative Process / Ex. 5

On Sep 13, 2018, at 4:18 PM, Konkus, John <konkus.john@epa.gov> wrote:

Deliberative Process / Ex. 5

From: Jones, Enesta
Sent: Thursday, September 13, 2018 4:02 PM
To: Konkus, John <konkus.john@epa.gov>; Block, Molly <block.molly@epa.gov>; Abboud, Michael <abboud.michael@epa.gov>; Hewitt, James <hewitt.james@epa.gov>
Cc: Jones, Enesta <Jones.Enesta@epa.gov>; Lynn, Tricia <lynn.tricia@epa.gov>; Grantham, Nancy <Grantham.Nancy@epa.gov>
Subject: Open Inquiries, 9/13/18

Six Awaiting Approval:

From: "Lynn, Tricia" <lynn.tricia@epa.gov>
Date: September 13, 2018 at 3:36:17 PM EDT
To: Press <Press@epa.gov>
Subject: FOR REVIEW: AP (Ellen Knickmeyer) RE: LNT standards vs. threshold, hermetic standards (9/17)

Reporter is asking about LNT standards vs. threshold, hermetic standards for radiation exposure. Ellen Knickmeyer, AP.

Deliberative Process / Ex. 5

Deliberative Process / Ex. 5

From: Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
Sent: Thursday, September 13, 2018 10:33 AM
To: Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
Cc: Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
Subject: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hello – wanted to also ask, is this still EPA policy?
https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
"Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."

"Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."

Best,
Ellen

From: Knickmeyer, Ellen
Sent: Thursday, September 13, 2018 10:06 AM
To: 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>

Cc: 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
Subject: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts: "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 4/20/2018 4:24:17 PM
To: Edward Calabrese [edwardc@schoolph.umass.edu]
Subject: Re: see improved statement of support-Ed Calabrese

Thanks so much!

On Apr 20, 2018, at 11:21 AM, Edward Calabrese <edwardc@schoolph.umass.edu> wrote:

> The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses
> In toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process. Confidence in the continued use of the LNT model
> as a default in cancer risk assessment has been seriously eroded by advances in modern molecular toxicology. These new findings strongly support this EPA proposal
> and its goal to place cancer risk assessment on an improved scientific foundation. Continuing reliance on the LNT as the default in cancer risk is not scientifically defensible.

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 4/19/2018 1:51:21 PM
To: Edward Calabrese [edwardc@schoolph.umass.edu]
Attachments: Data Access Draft - EPA - 4-17-18 - CLEAN.docx

Thanks!

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 10/2/2018 7:13:24 PM
To: Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]; Dominguez, Alexander [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5ced433b4ef54171864ed98a36cb7a5f-Dominguez,]
Subject: APNewsBreak: EPA says a little radiation may be healthy

We've asked for a retraction

https://apnews.com/

APNewsBreak: EPA says a little radiation may be healthy

WASHINGTON (AP) — The Trump administration is quietly moving to weaken U.S. radiation regulations, turning to scientific outliers who argue that a bit of radiation damage is actually good for you — like a little bit of sunlight.

The government's current, decades-old guidance says that any exposure to harmful radiation is a cancer risk. And critics say the proposed change could lead to higher levels of exposure for workers at nuclear installations and oil and gas drilling sites, medical workers doing X-rays and CT scans, people living next to Superfund sites and any members of the public who one day might find themselves exposed to a radiation release.

The Trump administration already has targeted a range of other regulations on toxins and pollutants, including coal power plant emissions and car exhaust, that it sees as costly and burdensome for businesses. Supporters of the EPA's new proposal argue the government's current no-tolerance rule for radiation damage forces unnecessary spending for handling exposure in accidents, at nuclear plants, in medical centers and at other sites.

"This would have a positive effect on human health as well as save billions and billions and billions of dollars," said Edward Calabrese, a toxicologist at the University of Massachusetts who is to be the lead witness at a congressional hearing Wednesday on EPA's proposal.

Calabrese, who made those remarks in a 2016 interview with a California nonprofit, was quoted by EPA in its announcement of the proposed rule in April. He declined repeated requests for an interview with The Associated Press. The EPA declined to make an official with its radiation-protection program available.

The regulation change is now out for public comment, with no specific date for adoption.

Radiation is everywhere, from potassium in bananas to the microwaves popping our popcorn. Most of it is benign. But what's of concern is the higher-energy, shorter-wave radiation, like X-rays, that can penetrate and disrupt living cells, sometimes causing cancer.

As recently as this March, the EPA's online guidelines for radiation effects advised: "Current science suggests there is some cancer risk from any exposure to radiation."

"Even exposures below 100 millisieverts" — an amount roughly equivalent to 25 chest X-rays or about 14 CT chest scans — "slightly increase the risk of getting cancer in the future," the agency's guidance said.

But that online guidance — separate from the rule-change proposal — was edited in July to add a section emphasizing the low individual odds of cancer: "According to radiation safety experts, radiation exposures of ...100 millisieverts usually result in no harmful health effects, because radiation below these levels is a minor contributor to our overall cancer risk," the revised policy says.

Calabrese and his supporters argue that smaller exposures of cell-damaging radiation and other carcinogens can serve as stressors that activate the body's repair mechanisms and can make people healthier. They compare it to physical exercise or sunlight.

Mainstream scientific consensus on radiation is based on deceptive science, says Calabrese, who argued in a 2014 essay for "righting the past deceptions and correcting the ongoing errors in environmental regulation."

EPA spokesman John Konkus said in an email that the proposed rule change is about "increasing transparency on assumptions" about how the body responds to different doses of dangerous substances and that the agency "acknowledges uncertainty regarding health effects at low doses" and supports more research on that.

The radiation regulation is supported by Steven Milloy, a Trump transition team member for the EPA who is known for challenging widely accepted ideas about manmade climate change and the health risks of tobacco. He has been promoting Calabrese's theory of healthy radiation on his blog.

But Jan Beyea, a physicist whose work includes research with the National Academies of Science on the 2011 Fukushima nuclear power plant accident, said the EPA proposal on radiation and other health threats represents voices "generally dismissed by the great bulk of scientists."

The EPA proposal would lead to "increases in chemical and radiation exposures in the workplace, home and outdoor environment, including the vicinity of Superfund sites," Beyea wrote.

At the level the EPA website talks about, any one person's risk of cancer from radiation exposure is perhaps 1 percent, Beyea said.

"The individual risk will likely be low, but not the cumulative social risk," Beyea said.

"If they even look at that — no, no, no," said Terrie Barrie, a resident of Craig, Colorado, and an advocate for her husband and other workers at the now-closed Rocky Flats nuclear-weapons plant, where the U.S. government is compensating certain cancer victims regardless of their history of exposure.

"There's no reason not to protect people as much as possible," said Barrie.

U.S. agencies for decades have followed a policy that there is no threshold of radiation exposure that is risk-free.

The National Council on Radiation Protection and Measurements reaffirmed that principle this year after a review of 29 public health studies on cancer rates among people exposed to low-dose radiation, via the U.S. atomic bombing of Japan in World War II, leak-prone Soviet nuclear installations, medical treatments and other sources.

Twenty of the 29 studies directly support the principle that even low-dose exposures cause a significant increase in cancer rates, said Roy Shore, chief of research at the Radiation Effects Research Foundation, a joint project of the United States and Japan. Scientists found most of the other studies were inconclusive and decided one was flawed.

None supported the theory there is some safe threshold for radiation, said Shore, who chaired the review.

If there were a threshold that it's safe to go below, "those who profess that would have to come up with some data," Shore said in an interview.

"Certainly the evidence did not point that way," he said.

The U.S. Food and Drug Administration, which regulates electronic devices that emit radiation, advises, broadly, that a single CT scan with a dose of 10 millisieverts may increase risks of a fatal cancer by about 1 chance in 2,000.

The EPA tucked its proposed relaxation of radiation guidelines into its "transparency in science" proposal in April. The proposal would require regulators to consider "various threshold models across the exposure range" when it comes to dangerous substances.

While the EPA rule change doesn't specify that it's addressing radiation and chemicals, the EPA's official press release announcing the change does.

Supporters of the proposal say it's time to rethink radiation regulation.

"Right now we spend an enormous effort trying to minimize low doses" at nuclear power plants, for example, said Brant Ulsh, a physicist with the California-based consulting firm M.H. Chew and Associates. "Instead, let's spend the resources on minimizing the effect of a really big event."

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 8/3/2018 9:14:55 PM
To: Woods, Clint [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bc65010f5c2e48f4bc2aa050db50d198-Woods, Clin]
Attachments: drp-10-209.pdf; ATT00001.txt

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3375488/pdf/drp-10-209.pdf

Dose-Response, 10:209–218, 2012
Formerly Nonlinearity in Biology, Toxicology, and Medicine

ISSN: 1559-3258
DOI: 10.2203/dose-response.11-040.Cox

International Dose-Response Society
www.dose-response.org

HORMESIS FOR FINE PARTICULATE MATTER (PM 2.5)

Louis Anthony (Tony) Cox, Jr. □ Cox Associates, University of Colorado

□ The hypothesis of hormesis – that substances that harm health at high exposures can reduce risks below background at low exposures, e.g., if they activate defenses without overwhelming them – becomes important for practical policy making if it holds for regulated substances. Recently, the U.S. EPA concluded that reductions in ambient concentrations of fine particulate matter (PM2.5) in air caused trillions of dollars worth of human health benefits for a compliance cost of only about $65 billion per year. This conclusion depends on an unverified assumption of a positive, causal, straight-line relation between PM2.5 concentrations and mortality risks. We review empirical data on PM2.5 and mortality risks (and their precursors, inflammatory responses) and conclude that the PM2.5 concentration-response relation may be J-shaped, rather than linear. This possibility implies that the 1990 Clean Air Act Amendment may well have produced no (or negative) human health benefits, rather than the trillions of dollars worth of reduced mortalities ascribed to it by EPA; and that attempts to achieve further risk-reduction benefits by further reducing PM2.5 concentrations may be counterproductive. This creates a very high value for scientific information that better reveals the true shape of the PM2.5 concentration-response function at and below current ambient levels.

Key words: PM2.5, hormesis, Clean Air Act, air pollution health effects, uncertainty analysis, risk-cost-benefit analysis, Weibull uncertainty distribution

INTRODUCTION

A strong form of the hypothesis of hormesis in toxicology and disease biology states that exposures to sufficiently small concentrations or exposure rates of agents that cause harm at higher levels are typically beneficial, reducing rates of disease or adverse effects below their background levels. A commonly postulated and observed general mechanism for hormesis is that low levels of exposure activate defensive mechanisms without overwhelming them, while higher levels saturate, deplete, or down-regulate the defenses, causing injury. For example, studies of the etiology of lung injury and diseases resulting from exposures to particulates in air have shown that high, prolonged exposures to a variety of particulates induce a non-specific inflammatory response, characterized by an increase in production of reactive oxygen species (ROS) by alveolar macrophages and other lung cells (Janssen *et al.* 1992, Comhair and Erzurum 2002, Azad *et al.* 2008). Low levels of exposure stimulate a compensating production of antioxidants (Janssen *et al.* 1992, Comhair and

Address correspondence to Dr. Tony Cox, 503 Franklin Street, Denver, Colorado, 80218; Email: tcoxdenver@aol.com

Erzurum 2002) that may compensate – or, if hormesis is correct, more than compensate – for increased ROS production, but experiments in rats show that higher levels of exposure overwhelm and down-regulate this limited defensive capacity, shifting the balance of oxidants and antioxidants toward an abnormally high-ROS environment that may then increase the risks of a variety of lung diseases, from emphysema to lung cancer (Azad *et al.* 2008). Such a mechanistic account naturally suggests that the concentration-response (C-R) function for particulate matter (PM) may have an effective threshold, or a hormetic (U-shaped or J-shaped) shape with a nadir, below which further reductions in exposure concentration, C, do not produce further reductions (and may even increase) the rates of adverse health responses, R.

If the hypothesis of hormesis is to play an important role in informing and improving national science-policy decisions about risk management of low-concentration exposures, it must be evaluated in the context of important real-world risk assessments and risk management decisions. A recent assessment by the United States Environmental Protection Agency (EPA) concluded that further reductions in fine particulate matter (PM2.5) in air are certain to produce further reductions in mortality risks (EPA, 2011) – more specifically, by an amount described by a Weibull uncertainty distribution, which puts zero probability mass on zero and negative values for the slope of the concentration-response relation at low exposure concentrations. This assessment provides an ideal opportunity to examine the plausibility of hormesis for PM2.5. EPA's analysis assumes that the C-R relation between PM2.5 concentrations (C) and mortality risks (R) is well described at low (e.g., present and future) ambient exposure levels by a straight-line, no-threshold function all the way down to the lowest measurable levels. According to this assumption, the C-R relation can be characterized by a single number, the slope of this line, called the C-R coefficient. EPA's uncertainty analysis puts a subjective probability of 100% on positive values for the C-R coefficient, implying that hormesis has zero probability of correctly describing the C-R function for PM2.5. The purpose of this paper is to re-examine this assumption in light of available data, and to re-evaluate whether hormesis might after all give a correct description of the PM2.5 C-R data.

If hormesis turns out to provide a correct description, or even a plausible possibility, for PM2.5, it has crucially important policy implications. Instead of accepting EPA's assumption that further reductions in PM2.5 concentrations will necessarily produce (proportionate) reductions in mortality risks and gains in life expectancy, hormesis would imply that there is an optimal exposure level (which we might have already passed) below which further reductions in PM2.5 concentrations produce no additional gains in public health – let alone the trillions of dollars of health benefits per year projected by EPA. Indeed, at sufficiently low

ambient concentrations, further reductions in PM2.5 could even be associated with modest increases in mortality rates, implying a negative C-R relation. This would require rethinking the wisdom and prudence of continuing to spend resources (estimated by EPA as about $65 billion per year in compliance costs) to reduce PM2.5 concentrations in order to seek hypothesized health benefits that may only become more remote as they are pursued.

META-ANALYSIS OF PM2.5-MORTALITY STUDIES SHOWS BOTH POSITIVE AND NEGATIVE ASSOCIATIONS, SUGGESTING A POSSIBLE J-SHAPED RELATION

Over 100 epidemiological studies have now estimated the concentration-response (C-R) coefficient in regression models of all-cause and cause-specific mortality rates regressed against ambient PM2.5 concentrations and other covariates. A puzzling feature of these studies has been that a sizable minority of them report statistically significant *negative* C-R coefficients, i.e., higher concentrations of PM2.5 are associated with significantly lower mortality rates, even though more report statistically significant positive coefficients. Nearly a decade ago, Dominici *et al.* (2002) found 20 non-significant negative C-R coefficients among 88 cities, although most coefficients in that study (positive and negative) were not statistically significant, due to limitations in sample sizes. Thus, the negative coefficients might have been due to sampling error. However, a more recent review (Franklin *et al.* 2007) found negative C-R coefficients for all-cause mortality and PM2.5 in one third (9 of 27) U.S. communities, with several being statistically significant (including Birmingham, Dallas, and Houston). Although it has been common practice to simply pool results across locations, and to conclude that the pooled mean C-R coefficient is significantly positive (since the 2/3 majority of positive coefficients outweighs the 1/3 of negative ones), this does not resolve the puzzle of why so many locations report negative coefficients.

If the statistical models being used are even approximately correct, then finding multiple statistically significant negative coefficients among 27 locations suggests that negative associations between PM2.5 and mortality rates really do occur. The same logic suggests that the multiple significant positive coefficients are also real. To reconcile these opposing conclusions, it is natural to assume that they are two parts of a larger, non-monotonic relation, e.g., a J-shaped or U-shaped function, with ascending and descending segments. In this case, locations with a high proportion of exposures on the descending part of the C-R relation will have negative average C-R coefficients, while locations with a high proportion of exposures on the ascending portion will have positive average C-R coefficients. Averaging the C-R coefficients across locations is not sensible, however, if the response to changes in concentrations is highly location-spe-

cific – as, indeed, appears to be the case. For example, an examination of C-R curves (rather than assumed constant C-R slope coefficients) for PM10 data in the twenty largest U.S. cities identified U-shaped curves in some cities, although this information was lost when the curved were averaged across cities (Daniels *et al.* 2000).

EPIDEMIOLOGICAL DATA ARE AMBIGUOUS, BUT NOT INCONSISTENT WITH HORMESIS

Evidence for negative, as well as positive, association between PM2.5 concentrations and mortality rates also arises from analyses that take into account model uncertainty by considering *multiple plausible models*, rather than selecting any single model (which would almost certainly be incorrect, given the large number of alternative statistical models that fit the data approximately equally well). Bayesian Model-Averaging (BMA) is one of the best-developed of such "ensemble" methods for using multiple models to reduce model-selection biases and to make more accurate risk predictions and uncertainty characterizations than any single regression model is likely to achieve. Applied to data from 11 Canadian cities, BMA indicates that both total suspended particulate (TSP) and ozone have statistically significant *negative* associations with mortality rates (Koop *et al.* 2007). Similar findings of negative associations for ozone have been reported in the United States (Joseph 2008).

To independently check the validity of such previously published reports of negative C-R relations, one may examine the iHAPSS (internet-based Health and Air Pollution Surveillance System) data base of pollutant levels and mortality rates for U.S. cities made available on-line by Johns Hopkins at www.ihapss.jhsph.edu/. Figure 1 shows plots of cause-specific mortality rate vs. deciles of estimated PM2.5 concentrations. (The data are reconstructed from preprocessed NMMAPS data posted at the website, which documents the smoothing procedure used to preprocess the raw data and the resulting possibility of negative values when data are reconstructed by adding back the smoothed mean. The NMMAPS documentation defines all-cause mortality (*death*) as excluding accidents.) The plots pool data across time (daily data from 1987 to 2000, although different cities started reporting in different years) and across the ten largest metropolitan area in the data base (Chicago, Dallas/Fortworth, Detroit, Houston, LA, Miami, New York, Phoenix, San Diego, and Santa Ana/Anaheim.)

The plots do not suggest any significant positive relations between PM2.5 and excess mortality risk at the lowest exposure concentrations (except possibly for COPD, which is a relatively small contributor to death rates); if anything, they are consistent with a weak negative or U-shaped association between exposures and cause-specific mortality risks for cardiovascular disease (CVD) and pneumonia/influenza mortality risks at the

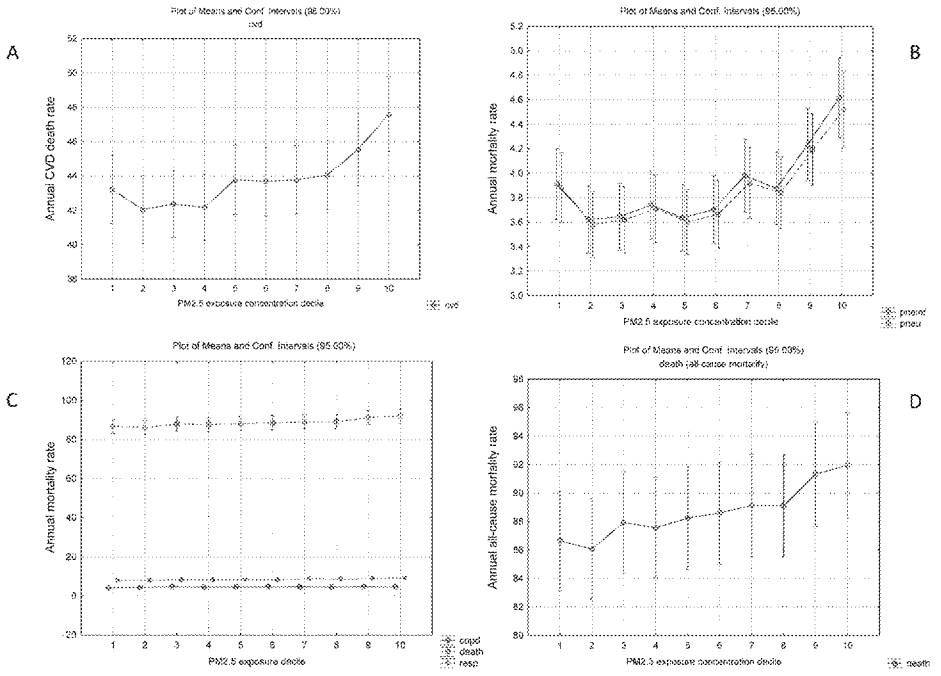


FIGURE 1. PM2.5 and Mortality Rate C-R Relations in Ten U.S. Cities. C-R relations for annual mortality rates: A = cardiovascular disease (CVD); B = pneumonia (pne) and pneumonia/influenza (pneuinf); C = all-case (death), chronic obstructive pulmonary disease (COPD), and respiratory (resp); D = all-cause mortality (expanded from C).

low (left) end of the PM2.5 exposure concentration distribution. The highest (right-most) deciles of the PM2.5 exposure concentration distribution do show increased risks, but it would be inappropriate to extrapolate these linearly down to zero, given the U-shapes of the empirical C-R relations between exposure concentrations (C) and mortality rates (R).

In multivariate regression analyses, other explanatory variables in the date set (especially year, month of year (with the winter months of December-February being high-risk months as well as high-pollution months), and minimum temperature) are all highly statistically significant predictors of all-cause and cardiovascular disease mortality rates in different age categories. PM2.5, too, is a strong predictor of all-cause and CVD mortality rates. After conditioning on other variables, however, no positive statistical effect of PM2.5 on mortality rates remains. For example, Table 1 shows the results of a multiple linear regression model fit to the data (using the commercial statistical software environment *Statistica 9.0*. The *b* coefficients are the ordinary least squares regression coefficients, and the *b** coefficient are their standardized values. The variable *Dec-Feb* is a binary variable with value 1 for these three months and 0 for other months.) Both estimated PM2.5 exposure (*pm25Reconstruct*) and all-cause mortality rates are highest in the winter months: the variable Dec-Feb is a con-

TABLE 1. Multiple Linear Regression Model for All-Cause Mortality Rates in 10 Cities

Regression Summary for Dependent Variable: death (all causes) R= .41 R?= .17 Adjusted R?= .17						
N=22242	b*	Std.Err. of b*	b	Std.Err. of b	t(22235)	p-value
Dec-Feb	0.16	0.007	31.66	1.50	21.2	0.000000
tmin	0.15	0.008	0.83	0.04	20.0	0.000000
Year	0.02	0.006	0.35	0.14	2.6	0.009320
Month	-0.02	0.006	-0.47	0.16	-3.0	0.002524
pm25Reconstruct	-0.02	0.006	-0.18	0.05	-3.4	0.000589
pHisp	-0.43	0.007	-226.40	3.47	-65.3	0.000000
Intercept			-619.44	270.48	-2.3	0.022023

founder that explains a positive univariate association between them, as shown in Figure 1D. However, in the multivariate model in Table 1, the coefficient of PM2.5 exposure is significantly *negative*, suggesting that, apart from such confounding, PM2.5 exposure does not increase mortality rates. Although, any such ecological regression (with unknown individual exposures) must be interpreted with caution, it is noteworthy that the apparent positive association between PM2.5 and mortality in Figure 1D is entirely removed by controlling for other variables in multivariate analysis, leaving a negative association at sufficiently low exposure concentration (and hence hormesis, overall) as a viable possibility.

Table 2 shows analogous results specifically for CVD mortality rates. Although both all-cause and CVD mortality rates are significantly predicted by month of year, as well as year (as mortality rates fall and life expectancies rise over time), minimum temperature (tmin), and proportion of Hispanics in the population, it is conspicuous that PM2.5 (the *pm25reconstruct* variable) has no significant positive relation with either mortality rate. The same is true in non-linear (e.g., polynomial regression and classification tree) models with interaction effects, for lagged values of PM2.5, and for other health end points, including respiratory mortality rate: *PM2.5 at ambient levels is not significantly positively associated with any adverse health outcomes.* This observation for ten U.S. cities is generally consistent with the results of Koop and Tole (2004) for Toronto.

Although reports of mixed positive and negative associations of PM2.5 concentrations with mortality rates are common in the literature (Daniels *et al.* 2000, Franklin *et al.* 2007, Koop *et al.* 2007, Joseph 2008), and although they may suggest a possible U-shaped or J-shaped relation between exposure concentrations and mortality rates, epidemiological studies are generally too weak and ambiguous to decisively reveal the true shape of the concentration-response function. Principal reasons include the lack of reliable measurements of individual exposures and lack of complete identification and control of confounders, both of which cast

TABLE 2. Multiple Linear Regression Model for Cardiovascular Mortality Rate

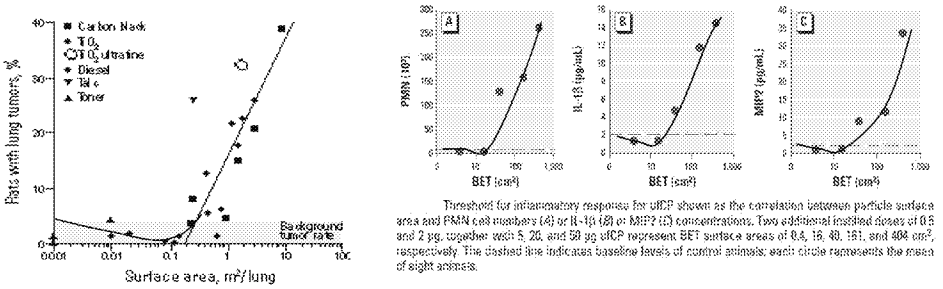
Regression Summary for Dependent Variable: cvd R= .37 R?= .14 Adjusted R?= .14						
N=22242	b*	Std.Err. of b*	b	Std.Err. of b	t(22235)	p-value
Dec-Feb	0.14	0.01	15.53	0.85	18.2	0.000000
tmin	0.12	0.01	0.36	0.02	15.0	0.000000
pm25Reconstruct	-0.01	0.01	-0.06	0.03	-1.8	0.068621
Month	-0.02	0.01	-0.22	0.09	-2.4	0.016366
Year	-0.05	0.01	-0.56	0.08	-7.3	0.000000
pHisp	-0.38	0.01	-110.64	1.98	-55.8	0.000000
Intercept			1170.99	154.60	7.6	0.000000

severe doubt on statistical estimates and inferences obtained by plugging estimated city-level exposures into regression or time series models as presumed explanatory variables (Sheppard *et al.* 2011). In addition, statistical associations (of any sign) need not necessarily reflect causality. Therefore, is desirable to consider toxicological dose-response data, to see whether a J-shaped relation is consistent with experimental data.

EXPERIMENTAL DATA SHOW J-SHAPED CONCENTRATION-RESPONSE RELATIONS

Experimental studies in human volunteers, including asthmatics, have led some commentators to conclude that, "[T]he weight of the evidence from controlled studies with animals and human volunteers suggests that PM is unlikely to cause premature death or other serious health effects at levels found in real-world air" (Schwartz 2007). This is consistent with earlier conclusions that, "It remains the case that no form of ambient PM — other than viruses, bacteria, and biochemical antigens — has been shown, experimentally or clinically, to cause disease or death at concentrations remotely close to US ambient levels" (Green and Armstrong 2003). To test such reassuring-looking conclusions more carefully, it is instructive to examine the concentration-response relations for particulate matter in animals, where concentrations have been varied systematically from low levels, at which no adverse effects are observed, to much higher levels at which inflammation in mice and rats, and fibrosis and lung tumors in rats, can be induced.

Figure 2 summarizes two sets of experimental data. The left panel shows lung tumor responses in rats (the only species that develops them) in response to varying concentrations of different types of particulates. The mechanism of tumor induction involves overwhelming of antioxidant and clearance defenses, unresolved chronic inflammation, repetitive injury to lung tissue, and fibrosis, scarring, and proliferation leading to tumors (Azad *et al.* 2008, Oberdörster 1997). The three right panels



Rat tumors (adapted from Oberdorster 1997) Mouse inflammation markers (adapted from Stoeger et al. 2006)

FIGURE 2. Rat tumor (left-most) and mouse inflammation (right) responses to PM. Original figures reproduced with permission from *Environmental Health Perspectives,* www.ncbi.nlm.nih.gov/pmc/articles/PMC1392224/figure/f3-ehp0114-000328/, doi: 10.1289/ehp.8266 and www.ncbi.nlm.nih.gov/pmc/articles/PMC1470142/?tool=pubmed. J-shaped curves have been superimposed on the original figures.

show the responses of three inflammatory markers in mice, to different concentrations of ultrafine carbon particulates (ufCP).

In both experiments, the surface area of particles in the lung is used as a dose metric, since it is the best predictor of response (better than mass or volume of PM. The "BET" protocol referred to on the right side provides a way to quantify this surface area.) The original authors of these experimental studies interpreted their findings as showing a threshold exposure level, below which exposure did not increase risk of adverse responses (inflammation in mice, on the right; tumors in rats, resulting from unresolved inflammation and associated other effects, on the left). However, as indicated by the J-shaped cuves that we have superimposed on the data points, the data are actually more consistent with hormesis, i.e., a positive baseline level at zero exposure that is reduced by very low levels of exposure, but that increases above background at higher exposure concentrations. Thus, while there may indeed be an exposure concentration level below which risk of adverse effects is not greater than background, it is more accurate to interpret the J-shaped curves as indicating hormesis, rather than thresholds.

DISCUSSION AND CONCLUSIONS

EPA's assumption that the concentration-response (C-R) function relating changes in ambient exposure concentrations of fine particulate matter (PM2.5) is well-described by a straight line with a positive slope (with 100% confidence, based on a subjective Weibull uncertainty analysis that precludes zero and negative slopes from having positive subjective probabilities), poses a direct challenge to the hypothesis of hormesis. We have reexamined empirical evidence on the shape of the C-R function, and find that such certainty that a positive linear C-R relation provides a

better description that alternative, hormetic (J-shaped) relations is unjustified. A J-shaped relation provides one possible explanation for common reports in the literature of statistically significant negative, as well as positive, C-R coefficients. However, in the absence of more accurate and detailed information about individual exposures, as opposed to ambient exposures at monitoring locations, epidemiological data alone cannot decisively establish the true shape of the C-R function (Sheppard *et al.* 2011). In our own analysis of a data set made available for public analysis, there is no clear positive relation between PM2.5 and all-cause or cause-specific mortality rates, although cause-specific mortality rates are significantly correlated with each other.

Turning to toxicological data, the results are clearer: in animal studies with accurate exposure measurements for individual animals, it is clear that inflammatory responses (and tumors in rat lungs) are not increased by sufficiently low exposures, contrary to the low-dose linear no-threshold assumption. As shown in Figure 2, hormesis (J-shaped dose-response relations) provides a description of such data.

In conclusion, available evidence supports the hypothesis of hormesis more strongly than the hypothesis of a positive linear no-threshold model for PM2.5 and mortality risks. Experimental evidence (Figure 2) indicates hormesis as the hypothesis that best fits the data. Epidemiological data, although more ambiguous (Figure 1), is consistent with hormesis in meta-analyses, as evidenced by mixed positive and negative C-R coefficients.

However, it is not necessary to settle conclusively whether hormesis holds for PM2.5 in order for it to have major policy implications. Recent EPA estimates of the human health benefits from the 1990 Clean Air Act Amendment (EPA, 2011) are crucially dependent on the unverified assumption of a positive linear no-threshold C-R function for PM2.5. As soon as it is acknowledged that hormesis is at least a plausible possibility – so that assigning it a subjective probability of zero, as in EPA's benefit assessment, is not warranted by data – it follows that the true incremental human health benefits of the 1990 Clean Air Act Amendment could also be zero or negative in many locations. This changes the nature of the cost-benefit comparison presented to the public from an apparent certainty of large positive return, in which compliance costs of $65 billion per year are said to produce lower mortality risks among the elderly, valued by EPA at about two trillion dollars per year, to a revised comparison in which the expenditure of $65 billion per year in compliance costs may instead – with probability of greater than 50%, if hormesis is more plausible than low-dose linearity – produce zero or negative net health benefits in reducing mortality risks. Many policy-makers who would embrace the former description might reject the latter, or at least request much more information about the uncertainties and evidence on the shape of the C-R function for PM2.5 at and below current ambient levels.

Thus, the hypothesis of hormesis, which appears to be supported by experimental data and consistent with (but not decisively proved or refuted by) current epidemiological data, changes the policy evaluation of claimed marginal health benefits of the 1990 Clean Air Act Amendment from a clear win for the public to a possible loss. More careful evaluation of the true shape of the C-R function is needed to determine which is correct. However, that the hypothesis of hormesis is plausible for a major air pollutant such as PM2.5 already provides sufficient grounds to question regulatory benefits assessments, evaluations, and policies that assume that cleaner air necessarily reduces mortality risks, even at and below current ambient concentrations.

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Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 4/23/2018 4:43:35 PM
To: Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]
Subject: Fwd: Transparency/Data Access Statements of Support
Attachments: Science Transparency TPs cw.docx; ATT00001.htm

Begin forwarded message:

From: "Woods, Clint" <woods.clint@epa.gov>
Date: April 23, 2018 at 12:36:39 PM EDT
To: "Yamada, Richard (Yujiro)" <yamada.richard@epa.gov>
Subject: FW: Transparency/Data Access Statements of Support

From: Woods, Clint
Sent: Monday, April 23, 2018 10:23 AM
To: Bowman, Liz <Bowman.Liz@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; Gordon, Stephen <gordon.stephen@epa.gov>; Konkus, John <konkus.john@epa.gov>; Letendre, Daisy <letendre.daisy@epa.gov>; Schwab, Justin <schwab.justin@epa.gov>
Subject: RE: Transparency/Data Access Statements of Support

Below are 5 statements of support for the release, followed by contact info for two other scientists willing to speak to reporters on the issue. Attached are some talking points which may be helpful. We're talking to OIRA at 11:00 and should have a clean(er) version of proposed rule to share after that call. On the previously circulated signage, suggest not including anything with "honesty" – Thanks!

"IDEM supports transparency in rulemaking," **says Bruno Pigott, Commissioner of the Indiana Department of Environmental Management (IDEM)**. "Good, sound science leads to better regulations."

"I believe that transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science," **said Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the journal *Risk Analysis*.** "Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."

"EPA's proposed rule, Strengthening Transparency in Regulatory Science, is badly needed," **said Dr. Jason Scott Johnston, Director, Olin Law and Economics Program, University of Virginia School of Law.** "Best practice among peer-edited scientific journals is to require that data and statistical routines used in published papers be posted online and/or made publicly available. To apply the same standards to research that EPA says justify regulations affecting billions of dollars in economic activity and millions of human lives is essential for those regulations to truly be scientifically based."

"In the development of regulations based on environmental studies, numerous subjective assumptions and choices must be made regarding the selection of data and models that have a profound impact on the strength of any statistical associations and even whether the associations are positive or negative. The appropriateness of the assumptions and choices are not adequately evaluated in the standard peer review process. That is why it is essential that the data and models be placed in the public domain for a more rigorous evaluation by qualified experts. The proposed regulation, Strengthening Transparency in Regulatory Science, will provide an opportunity for such evaluations," **said Dr. George Wolff, Principal Scientist, Air Improvement Resource, Inc., and former Chairman of EPA's Clean Air Scientific Advisory Committee (1992 – 1996).**

"The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process," **stated Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts**

Deliberative Process / Ex. 5

From: Bowman, Liz
Sent: Friday, April 20, 2018 3:29 PM
To: Woods, Clint <woods.clint@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; Gordon, Stephen <gordon.stephen@epa.gov>; Konkus, John <konkus.john@epa.gov>; Letendre, Daisy <letendre.daisy@epa.gov>; Schwab, Justin <Schwab.Justin@epa.gov>
Subject: RE: Transparency/Data Access Statements of Support

That would be great, can you send us what you have, as well as the draft of the policy/proposed rule? I can work on the draft press release and talking points, while Daisy/Stephen focus on planning the event with John.

From: Woods, Clint
Sent: Friday, April 20, 2018 2:21 PM
To: Bowman, Liz <Bowman.Liz@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; Gordon, Stephen <gordon.stephen@epa.gov>; Konkus, John <konkus.john@epa.gov>; Letendre, Daisy <letendre.daisy@epa.gov>; Schwab, Justin <Schwab.Justin@epa.gov>
Subject: Transparency/Data Access Statements of Support

Happy to work on some talking points for a release to accompany Tuesday's announcement.

We should have 2-3 sentence statements of support from:

- Jason Scott Johnston, PhD/JD, Director, Olin Law and Economics Program, University of Virginia School of Law
- Edward J. Calabrese, PhD, Professor, Environmental Health Sciences, University of Massachusetts

- Louis Anthony (Tony) Cox, Jr., PhD, President, Cox Associates, Member, National Academy of Engineering, Editor-in-Chief, *Risk Analysis*
- Bruno Pigott, Commissioner, Indiana Department of Environmental Management
- George Wolff, PhD, Former Chair of EPA's Clean Air Scientific Advisory Committee (1993 – 1996)

A few examples:

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 4/23/2018 2:24:58 PM
To: Szabo, Aaron L. EOP/CEQ Personal Matters / Ex. 6
Subject: RE: EPA - Data Access NPRM - comments

Still waiting on draft press release, but below are statements of support which will be included:

"IDEM supports transparency in rulemaking," **says Bruno Pigott, Commissioner of the Indiana Department of Environmental Management (IDEM)**. "Good, sound science leads to better regulations."

"I believe that transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science," **said Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the journal *Risk Analysis*.** "Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."

"EPA's proposed rule, Strengthening Transparency in Regulatory Science, is badly needed," **said Dr. Jason Scott Johnston, Director, Olin Law and Economics Program, University of Virginia School of Law.** "Best practice among peer-edited scientific journals is to require that data and statistical routines used in published papers be posted online and/or made publicly available. To apply the same standards to research that EPA says justify regulations affecting billions of dollars in economic activity and millions of human lives is essential for those regulations to truly be scientifically based."

"In the development of regulations based on environmental studies, numerous subjective assumptions and choices must be made regarding the selection of data and models that have a profound impact on the strength of any statistical associations and even whether the associations are positive or negative. The appropriateness of the assumptions and choices are not adequately evaluated in the standard peer review process. That is why it is essential that the data and models be placed in the public domain for a more rigorous evaluation by qualified experts. The proposed regulation, Strengthening Transparency in Regulatory Science, will provide an opportunity for such evaluations," **said Dr. George Wolff, Principal Scientist, Air Improvement Resource, Inc., and former Chairman of EPA's Clean Air Scientific Advisory Committee (1992 – 1996).**

"The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process," **stated Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts**

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 4/18/2018 6:16:44 PM
To: Edward Calabrese [edwardc@schoolph.umass.edu]
Subject: RE: Quick Question

Thanks so much – I will try you tomorrow morning. Is Personal Phone / Ex. 6 the best number?

From: Edward Calabrese [mailto:edwardc@schoolph.umass.edu]
Sent: Tuesday, April 17, 2018 8:25 PM
To: Woods, Clint <woods.clint@epa.gov>
Subject: RE: Quick Question

Dear Clint:

Thanks for the email....I would be able to talk on Thursday or Friday....mornings are usually best.

Ed

From: Woods, Clint <woods.clint@epa.gov>
Sent: Tuesday, April 17, 2018 1:00 PM
To: Edward Calabrese <edwardc@schoolph.umass.edu>
Subject: Quick Question

Dr. Calabrese,

I hope all is well! I know it has been a few years since we had the chance to work together on some risk science issues, but I wanted to check to see if you might have some free time in the next couple of days for a quick call to discuss a couple items related to transparency and default linear assumptions in EPA's work?

Thanks!

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

Message

From: Woods, Clint [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC65010F5C2E48F4BC2AA050DB50D198-WOODS, CLIN]
Sent: 9/24/2018 3:57:02 PM
To: Schwab, Justin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eed0f609c0944cc2bbdb05df3a10aadb-Schwab, Jus]
Subject: Fwd: New IQG Case: RFC 18003 - NATA/Ethylene Oxide
Attachments: RFC 18003 Request.pdf; ATT00001.htm

Begin forwarded message:

From: "Shoaff, John" <Shoaff.John@epa.gov>
To: "Wehrum, Bill" <Wehrum.Bill@epa.gov>, "Woods, Clint" <woods.clint@epa.gov>, "Tsirigotis, Peter" <Tsirigotis.Peter@epa.gov>, "Koerber, Mike" <Koerber.Mike@epa.gov>
Cc: "Lewis, Josh" <Lewis.Josh@epa.gov>
Subject: FW: New IQG Case: RFC 18003 - NATA/Ethylene Oxide

Bill et al,

Thought you might want to be aware of this new IQG case, see attached. Our QA poc, Tom Eagles, just received it from OEI and will likely touch base with Kelly R. in OAQPS for awareness and need for SME with request. Thx.

John

JOHN SHOAFF | DIRECTOR
OFFICE OF AIR POLICY & PROGRAM SUPPORT (OAPPS)
OFFICE OF AIR & RADIATION | U.S. EPA | WJC NORTH 5442-B
1200 PENNSYLVANIA AVE. NW | MC 6103A | WASHINGTON, D.C. | 20460 | USA
Shoaff.john@epa.gov | **1-202-564-0531 DIRECT | 1-202-257-1755 MOBILE**

From: Kirby, Kevin
Sent: Monday, September 24, 2018 10:05 AM
To: Eagles, Tom <Eagles.Tom@epa.gov>
Subject: New IQG Case: RFC 18003 - NATA/Ethylene Oxide

Good Morning Tom,
We just received a new RFC challenge dealing with the NATA framing of EO.
Could you please help me discern the SMEs for this so that I can get a Scoping Team meeting scheduled ASAP.
As you know, we stretch to get the response out within 90 days.
Thanks,
Kevin

Kevin J. Kirby
Enterprise Data Architect
US Environmental Protection Agency

OEI/OEIP/EQMD
202 566-1656 desk